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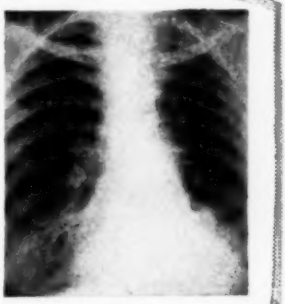

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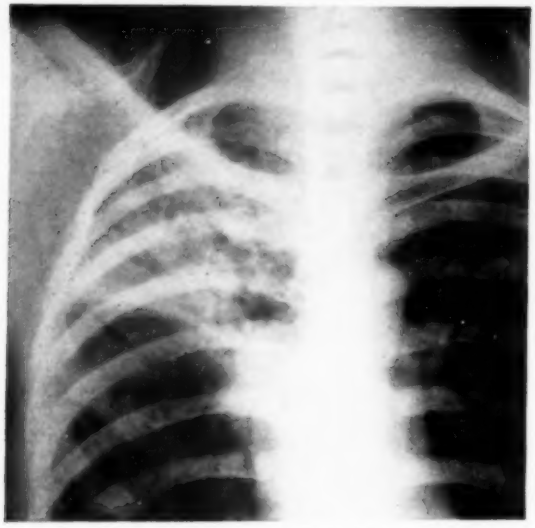

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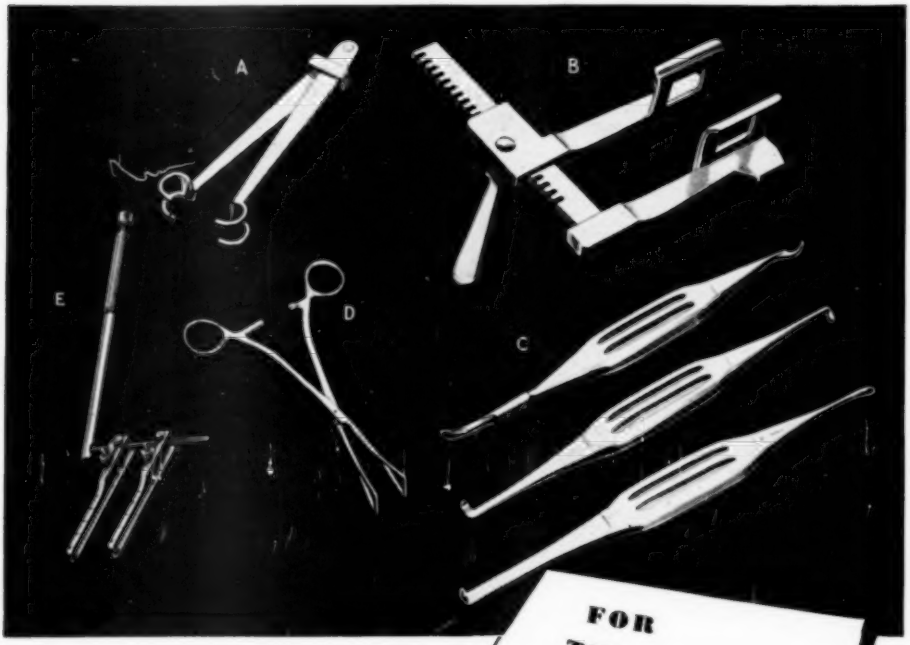

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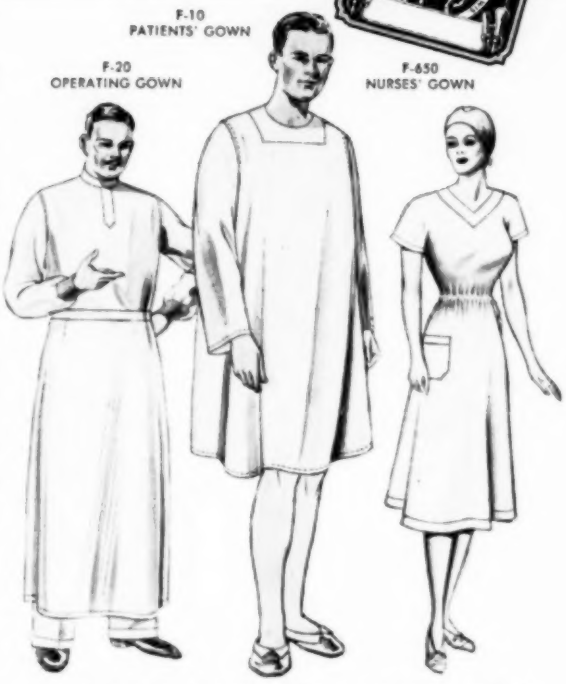

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INFLUENCE OF TYPE OF DISEASE ON THE RESULTS OF THORACOPLASTY IN PULMONARY TUBERCULOSIS[1]

MORRIS RUBIN AND ROBERT KLOPSTOCK

(Received for publication March 28, 1949)

INTRODUCTION

Extrapleural thoracoplasty is a well established procedure in the surgical treatment of pulmonary tuberculosis. The late results, however, still include a significant number of failures for an apparently standardized operation. Unsuccessful results are generally ascribed to poor choice of patients, insufficient collapse of the diseased lung, or to complications resulting from the operation itself. But in spite of more careful selection of patients and greater refinements in operative technique, there has not occurred a significant improvement in the results in recent years. Whether or not the picture has changed significantly since the introduction of streptomycin is a matter to be decided in the future.

The following report is an analysis of the early and late results of thoracoplasty in 168 patients with pulmonary tuberculosis operated upon at the Triboro Hospital over a period of five years, and followed from two to six years since the completion of the operation. In this analysis particular emphasis has been placed on the type of disease treated. The patients were subgrouped according to the predominant clinico-pathologic feature of the disease as determined from their records and serial chest roentgenograms prior to the thoracoplasty. The results of the operation within the individual groups were then studied and compared. The data were also reviewed for the group as a whole to permit a comparison of the results in this clinic with those obtained in other clinics. It was hoped that an analysis of the results in the manner outlined might be fruitful in establishing more precise indications and contraindications in the use of thoracoplasty and the other surgical procedures, such as pulmonary resection, which are currently employed in the treatment of pulmonary tuberculosis.

MATERIAL

From January 1941 until January 1946, extrapleural thoracoplasty was performed on 168 patients with pulmonary tuberculosis. The group included 107 males and 61 females and consisted of 153 white patients, 11 Negroes, 2 Chinese, and 2 Porto Ricans. Thoracoplasties performed for tuberculous empyema were excluded from the analysis. The operation was uniform throughout the series and consisted of the modern multi-staged, selective thoracoplasty. The number of stages and ribs resected depended upon the extent and location of the disease and the condition of the patient. The transverse processes were, as a rule, resected. An apicolysis was performed only in selected cases. Supplementary

[1] From the Surgical Service, Triboro Hospital, Jamaica, Long Island, New York.

operations such as anterior stages and revisions were performed, when indicated, to close residual cavities.

With the few exceptions to be noted later, the indication for thoracoplasty was the presence of cavitary pulmonary tuberculosis and tubercle bacilli in the sputum or gastric washings. In 5 patients the sputum became negative for tubercle bacilli prior to surgery but, because of poor family background and evidence of previous instability of the disease, thoracoplasty was considered advisable. Tomographic studies were done in almost every instance before and after surgery. Small cavities were occasionally discernible by tomography in the contralateral lung which were not detected in routine films. One hundred thirty-nine patients were bronchoscoped preoperatively. Pulmonary functional studies, including bronchospirometry, were performed in borderline cases, especially in the presence of bilateral disease or if there had been a history of contralateral

TABLE 1

Age Incidence

AGE	NUMBER OF PATIENTS
15 to 20	7
21 to 30	55
31 to 40	59
41 to 50	34
51 to 57	13
Total	168

disease that had required collapse treatment. All patients over 40 years of age were examined by a cardiologist before operation. None of the patients received streptomycin, as the operations were performed before this antibiotic came into general use.

Classification

To permit a more accurate analysis of the factors entering into the results, the 168 cases submitted to thoracoplasty were divided into groups based on the predominant clinico-pathologic feature of the disease as determined by serial roentgenograms and the clinical course. The determining factor in this classification was not the size of the cavity, but rather the underlying pathology leading to cavity formation. Large, thin-walled cavities were therefore differentiated not because of their size but because they represent a definite pattern of pulmonary tuberculosis. The fate of pulmonary cavities depends largely on their bronchocavitary dynamics, that is, the degree of stenosis of the draining bronchi traversing the cavity wall and the elasticity of the cavity wall itself, whether atelectatic or fibrotic.

Group I. *Fibrocaseous tuberculosis:* This group was characterized by predominantly productive lesions, limited in extent, associated with small or moderate-sized cavities. Active disease had usually existed one to two years and appeared clinically stabilized at the time of surgery. This group yields the largest number of cases treated with thoracoplasty.

Group II. *Fibroid tuberculosis:* Pulmonary disease with marked fibrosis and retraction of the involved lobes associated with rigid cavities, bronchiectasis, and emphysema was included in this category. The disease had usually existed for many years.

Group III. *Caseocavernous tuberculosis:* A few patients were found to have a progressive, caseating form of tuberculosis. They were submitted to thoracoplasty with the hope that the operation might halt the progress of the disease.

Group IV. *Tuberculosis associated with large thin-walled cavities:* Patients whose lungs contained large, thin-walled cavities were included in this group. Small disseminated tuberculous foci usually surrounded the cavity. Multiple cavities occasionally were present. As a rule, the patients were in good health.

Group V. *Tuberculosis and bronchiectasis:* This group consisted of patients with upper lobe fibroid tuberculosis and lower lobe bronchiectasis. This type of lesion is widely classified as the "destroyed lung." The bronchiectasis was not necessarily tuberculous in nature.

TABLE 2

Extrapleural Thoracoplasty: 168 Cases
Pathologic Pattern and Extent of Diseases

TYPE OF DISEASE	NUMBER CASES	DISTRIBUTION		
		Unilateral active		Bilateral active disease
		No Contralateral Disease	Contralateral inactive	
I. Fibrocaseous	117	37	60	20
II. Fibroid	13	2	10	1
III. Caseocavernous	5	2	3	0
IV. Giant cavity	23	6	17	0
V. Tuberculosis and bronchiectasis	6	3	2	1
VI. Unexpandable lung	4	3	1	0
Total	168	53	93	22

Group VI. *Unexpandable lung:* Patients in this group had previously had pneumothorax treatment, which had resulted in an unexpandable lung due to stenosis of a major bronchus. Unexpandable lung due to a pleural membrane was not noted since patients with pleural complications were excluded from this survey. Actually, the unexpandable lung is a complication of therapy rather than a type of pulmonary tuberculosis.

In table 2 may be seen the distribution of the cases according to the above classification. One hundred forty-six patients were found to have unilateral active disease, 93 of whom had evidence of inactive tuberculosis in the contralateral lung. Twenty-two patients had bilateral active tuberculosis.

RESULTS

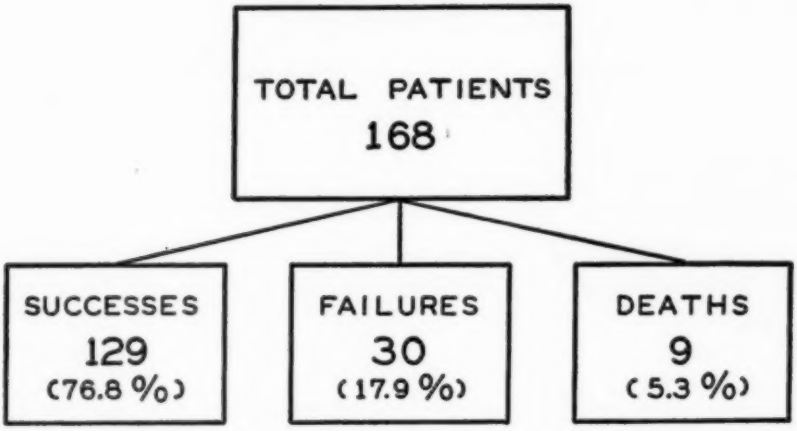
Combined Groups

Immediate results: The immediate results for the entire series of cases are summarized in table 3. The early results were based on the status of the patients six to eight weeks after the completion of the thoracoplasty when they were usually transferred to the medical service for further convalescence. The oper-

ation was considered "successful" when: (*1*) cavity closure was realized as determined by Bucky roentgenograms and tomograms; (*2*) sputum "conversion" was achieved on repeated sputum or gastric concentrates and cultures; and (*3*) respiratory function seemed adequate. Relative degrees of improvement were not classified. A thoracoplasty which failed to close the cavity and "convert" the sputum, or could not be completed because of a deterioration in the patient's status or as a result of respiratory insufficiency resulting from the operation, was considered a "failure." No case was classified as a failure, however, unless active disease was present following a thoracoplasty which could not be completed, or after attempts to control the disease by supplementary surgery, such as anterior stages or revisions, had failed. Thoracoplasty failures submitted to pulmonary resection were still classified as failures.

TABLE 3

Early Surgical Results



As may be seen in table 3, cavity closure and sputum "conversion" were achieved in 129 (76.8 per cent) of the 168 patients submitted to thoracoplasty. Residual cavitation and/or persistently "positive" sputum were found in 30 patients (17.9 per cent). Nine patients did not survive the operation, a mortality of 5.3 per cent. The postoperative complications are analyzed in table 4. Wound infections occurred in 25 patients. Postoperative spreads of disease occurred in 19 patients. In 13 instances, this complication occurred on the operated side and in 6 on the contralateral side. The fatalities are analyzed in table 5.

Late results: A recent follow-up report was obtained in 141 of the 168 patients two to six years following the operation. Twenty-seven patients could not be traced. Patients who were not attending the Triboro follow-up clinic were traced by questionnaires sent to hospitals, chest clinics, or private physicians. In table 6 is shown the present status of the patients traced. To present a comprehensive survey of the results, the early as well as the late fatalities are included.

Of 141 patients followed, 89 (63.1 per cent) are clinically well, the disease arrested. Thirty-two patients have active tuberculosis (22.7 per cent). In 20 of these 32 unsuccessful cases active tuberculosis is present on the operated side; in 12, in the contralateral lung. Of the 20 late failures with active disease beneath

TABLE 4

Postoperative Complications

Wound infections	25 (14.9 per cent)
Postoperative spreads	
Contralateral	6
Ipsilateral	13
Total	19 (11.3 per cent)
Miscellaneous	
Pleural tears	8
Cerebral vasc. acc.	2
Pleural effusions	3
Severe hemoptysis	1
Horner's syndrome	1
Wrist drop	1

TABLE 5

Analysis of Fatalities

Postoperative deaths	
Resp. insufficiency	4
Pulmonary embolism	2
Shock	1
Sepsis	1
Suicide	1
	9 (5.3 per cent)
Late deaths	
Progressive disease	7
Resp. insufficiency	2
Cocaine reaction	1
Undetermined	1
	11 (8.3 per cent)

the thoracoplasty, 15 had had early unsatisfactory results and persistently "positive" sputum. Active disease recurred in only 5 patients on the operated side. It should be noted that in most instances of reactivation of the disease in the untreated lung, nearly all had roentgenographic evidence of disease in that lung at the time of operation. There were 11 (8.3 per cent) late deaths (table 5). The fate of the early surgical failures and successes is shown in tables 7 and 8.

TABLE 6

Present Status of Patients

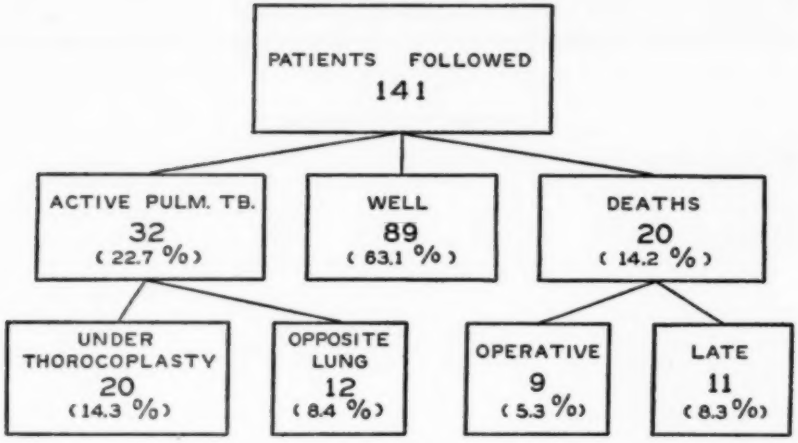
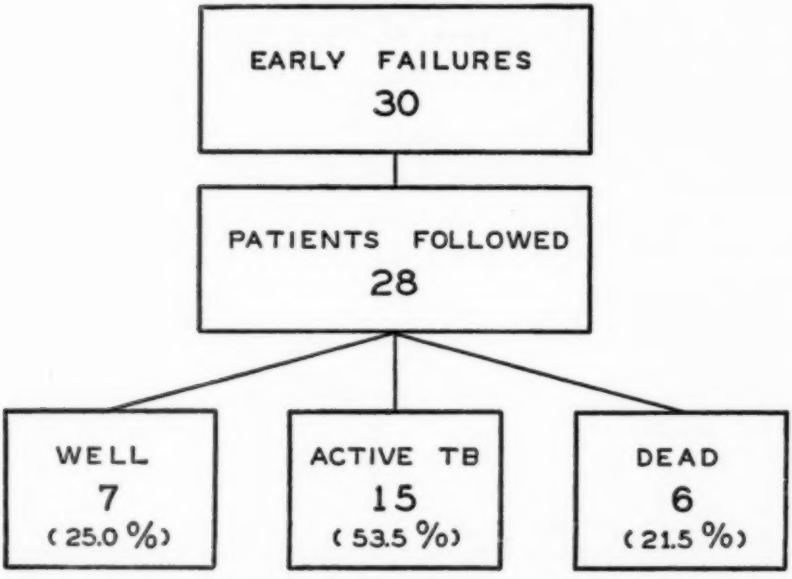


TABLE 7

Fate of Early Surgical Failures



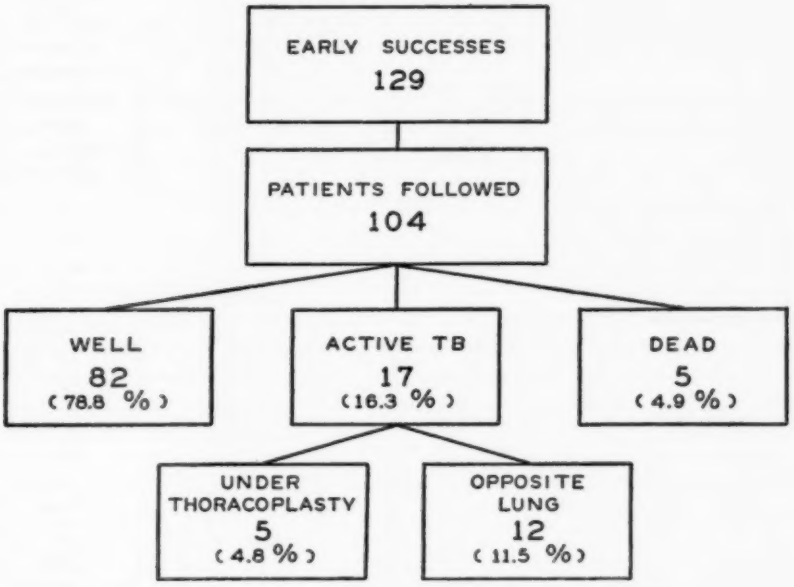
Late Results According to Clinico-pathologic Groups

Group I. *Fibrocaseous tuberculosis:* One hundred seventeen patients were found to have tuberculosis in which fibrosis predominated. Active disease was

usually limited to the upper portion of the lungs and showed little tendency to progress. Cavities, varying from 2 to 4 cm. in diameter, were demonstrable in almost every instance. Ninety-seven patients of this group were submitted to thoracoplasty for active disease in one lung. In 37 of these, the disease was unilateral; in 60, there were some arrested foci in the other lung. In 20 patients, there was bilateral active tuberculosis requiring bilateral collapse measures, the results of which will be analyzed separately. The immediate and late results in the 97 patients with unilateral, or predominantly unilateral, active disease are shown in table 9.

TABLE 8

Fate of Early Successes



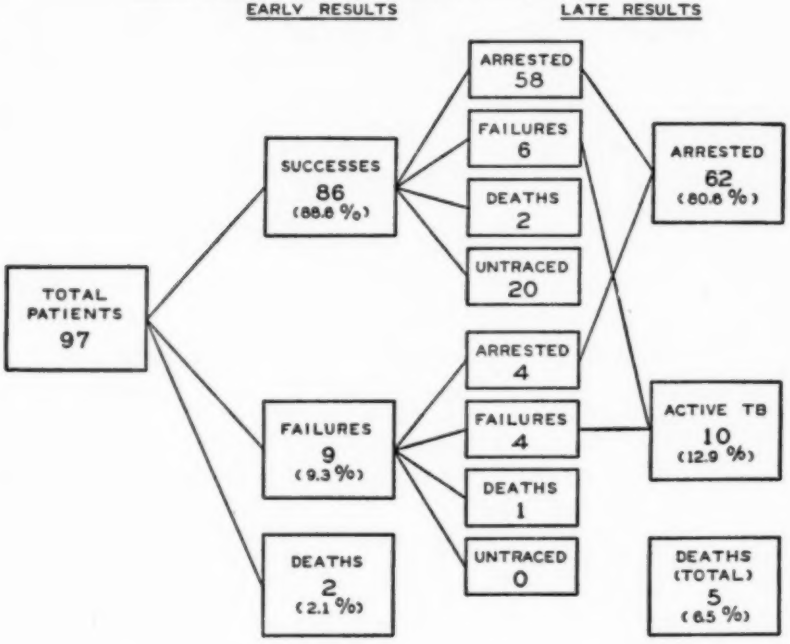
Early cavity closure and sputum "conversion" were attained by 86 patients (88.6 per cent). There were 9 early failures and 2 postoperative deaths. Seven of the 9 early failures were associated with delays in the completion of the operation as a result of wound infection in 6 and postoperative spread of disease in one. One of the deaths resulted from severe paradoxical respiration following the first stage; the other was due to pulmonary embolism, proved at autopsy, following an appendectomy performed two weeks after the first stage. The factor of interruptions will be discussed later.

The late results in 77 patients with unilateral active fibrocaseous tuberculosis reveal that 62 (80.6 per cent) are well and their disease is arrested. Of 10 patients with progressive tuberculosis, 5 have active lesions in the lung of the operated side and 5 have active lesions in the opposite lung. Four of the 5 patients with

active disease on the operated side were originally classified as early surgical failures. Four of the remaining 9 patients classified as early failures are well at present and one has died. In only one instance did a breakdown occur in the collapsed lung after a period of apparent arrest of the disease. All of the patients who developed active tuberculosis in the noncollapsed lung had evidence of inactive disease in that lung at the time of operation. There were 3 late deaths. Tuberculous meningitis accounted for one and another died suddenly from a

TABLE 9

Results Unilateral Active Fibrocaseous Tuberculosis, Group I



cocaine reaction preparatory to bronchoscopy. The cause of death in the third patient could not be ascertained.

Of the 20 patients with bilateral upper lobe fibrocaseous tuberculosis, not included in table 9, 13 were submitted to thoracoplasty in the presence of a contralateral pneumothorax. Sputum "conversion" and cavity closure occurred in 8 patients. There were 3 early failures. One patient developed a depressive psychosis, which precluded the completion of the thoracoplasty. Active disease persisted in 2 patients. There were 2 early deaths. One patient committed suicide and the other died from respiratory embarrassment following the first stage. At the present time only 2 patients are well. Five have active disease; 4 in the re-expanded lung and one under the thoracoplasty. There were 2 late deaths,

one of which was due to progressive disease, the other to a spontaneous tension pneumothorax. Two patients could not be traced.

Seven patients were submitted to bilateral thoracoplasty. There was one postoperative death following the initial stage of the contralateral thoracoplasty due to severe paradoxical respiration. Four patients with completed bilateral thoracoplasties had arrested disease. Two, however, were followed less than two years because of very long intervals between operations and were not classified with the arrested cases (table 11). There were no late deaths. Two patients could not be traced.

The patients with active fibrocaseous tuberculosis limited to one side responded very well to thoracoplasty. The majority were between twenty and forty years of age, were good surgical risks, and had adequate respiratory reserve. Patients with bilateral thoracoplasties did better than those with contralateral pneumothoraces. Late exacerbations in the re-expanded lung accounted for many of the failures.

Group II. *Fibroid tuberculosis:* This form of tuberculosis represents the late phase of the disease described in the previous group. It is characterized by marked fibrosis and distortion of the affected lobes. Pulmonary emphysema of varying degree and dislocation of mediastinal structures are frequent sequelae. The problem presented in this group is the closure of one or more rigid-walled cavities in individuals with impaired pulmonary function. Of the 13 patients in this group, 10 were over forty years of age; 3 were in their mid thirties.

Thoracoplasty was completed in only 6 of the 13 patients, with resulting cavity closure and sputum "conversion," one of whom had considerable dyspnea following the operation. Unsuccessful results were obtained in 5 patients, in 4 of whom dyspnea prevented the completion of the operation. A residual cavity and "positive" sputum were present in the fifth patient. There were 2 postoperative deaths. Massive pulmonary embolism proved at autopsy occurred in one patient and respiratory embarrassment after the first stage was fatal in another. Dyspnea was a frequent complication in this group, occurring in 6 of the 13 patients. At present, 5 patients can be considered well and 4 are alive with active disease. One late death occurred in one of the patients with an incomplete thoracoplasty as a result of increasing respiratory embarrassment. One patient could not be traced. As in the previous group, there were no deaths as a result of progressive tuberculosis. We have recently been considering pulmonary resection in selected patients with this form of tuberculosis.

Group III. *Caseocavernous tuberculosis:* Patients with caseocavernous tuberculosis are not suitable for thoracoplasty as a rule. Nevertheless, there were 5 patients with this form of disease who had improved sufficiently to warrant an attempt at thoracoplasty with the full realization of the risks involved. The operative course was stormy in all but one. At present, 2 patients have "negative" sputum but have dyspnea on exertion which, however, does not prevent them from working. The disease progressed in the remaining 3 patients, terminating fatally in one. It is possible that streptomycin may alter the prognosis in this group.

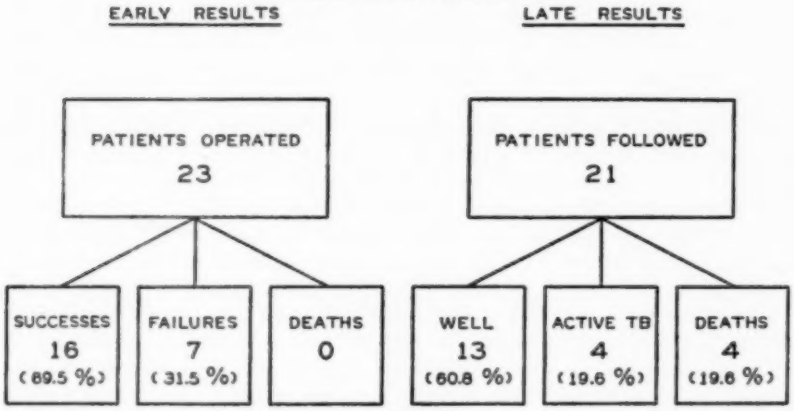
Group IV. *Tuberculosis associated with giant thin-walled cavitation:* A giant

cavity was the prominent feature of the disease in 23 patients. The cavity measured five or more centimeters in its greatest diameter, was thin-walled, and usually surrounded by disseminated disease. Large cavities due to massive caseation necrosis, which should be classified as caseocavernous tuberculosis, were not included in this group. Patients with such cavities seldom come to thoracoplasty because of the acute course of the disease. There were no instances of bilateral giant cavities. Of 17 patients bronchoscoped preoperatively, only 5 had visible endobronchial disease. One patient had laryngeal tuberculosis; the remaining 4, disease of the bronchus of the involved lobe. A study of resected specimens has revealed tuberculosis of the small bronchi in this type of lesion.

Intracavitary pressure readings performed in a number of instances disclosed the cavities to be of a tension type; a few had free bronchial communication. In

TABLE 10

Results Thin-walled Cavities, Group IV



several others periodic changes were noted in the bronchocavitary dynamics. In 17 patients, there was roentgenographic evidence of inactive disease in the contralateral lung. Monaldi suction was employed prior to thoracoplasty in 2 cases with diminution in the size of the cavity. Unfortunately, surgery could not be completed in either instance because of respiratory embarrassment following the first stage. One patient had amyloidosis but underwent the operation under local anaesthesia with satisfactory results. She died three years later following the development of another giant cavity of the same pattern in the contralateral lung.

Cavity closure and sputum "conversion" were achieved in 16 of the 23 patients (69.5 per cent). Seven patients (31.5 per cent) were left with residual cavities and sputum positive for tubercle bacilli. The thoracoplasty could not be completed in 4 patients because of insufficient respiratory reserve in 3 and severe asthmatic seizures in one. There were no postoperative deaths. Twenty-one of the

23 patients have been followed and 13 (60.8 per cent) are well. There were 4 late deaths (19.6 per cent), 2 resulting from contralateral disease with giant cavitation. Two of the 4 patients who were persistently dyspneic after the operation died subsequently. Four patients still have residual cavities and sputum positive for tubercle bacilli.

The difficulties encountered in obliterating giant cavities, especially those of the valvular variety, are shown by the amount of surgery required. There were more stages and more ribs resected in this group than in any of the other groups. Nine of the 19 patients, in whom the thoracoplasty was completed, underwent four or five operations and required resection of from 8 to 11 ribs to achieve cavity closure. Eleven of the 19 patients required supplementary stages and revisions.

TABLE 11

Late Results According to Groups

TYPE OF DISEASE	CASES FOLLOWED	ARRESTED TB.	ACTIVE TB.	DEATHS
I. Fibrocaseous				
Unilateral	77	62(80.6%)	10(12.9%)	5(6.5%)
Bilateral	16	4(25.0%)	7(43.8%)	5(31.2%)
II. Fibroid	12	5(41.7%)	4(33.3%)	3(25.0%)
III. Caseocavernous	5	2(40.0%)	2(40.0%)	1(20.0%)
IV. Giant Cavity	21	13(60.8%)	4(19.6%)	4(19.6%)
V. Tuberculosis and Bronchiectasis	6	0(0%)	4(66.6%)	2(33.4%)
VI. Unexpandable lung	4	3(75.0%)	1(25.0%)	0(0%)
Total	141	89(63.1%)	32(22.7%)	20(14.2%)

Group V. *Tuberculosis and bronchiectasis:* In 6 patients a combination of tuberculosis and bronchiectasis resulted in destruction of a lung. Symptoms referable to suppuration usually overshadowed those of active tuberculosis. Excessive cough and copious expectoration of purulent, occasionally foul-smelling sputum were particularly troublesome. Roentgenograms of the chest revealed a shrunken, destroyed lung with tuberculous cavities in the upper lobe and bronchiectasis in the remaining lobes. Four of the 6 patients had contralateral disease which was considered to be inactive at the time of operation. Thoracoplasty was unsatisfactory in every case. The operative course was stormy, in most instances because of retention of secretions which caused death in 2 patients. In a third individual, reactivation of disease in the opposite lung precluded completion of the operation. All 3 of the patients in whom thoracoplasty was completed are troubled with cough and purulent expectoration, although in one the sputum is negative for tubercle bacilli. None of the living can be considered well.

Group VI. *Unexpandable lung:* Bronchoscopic examination revealed stenosis of a main bronchus in 4 patients, all of whom had unexpandable lungs. They all had had pneumothorax treatment. In this series, none were found to have an unexpandable lung secondary to a pleural membrane, in view of the fact that

patients with pleural complications were not included. Attempts at re-expansion of the lung prior to thoracoplasty in one patient resulted in a marked shift of the mediastinum to the affected side. The operation was done in this instance to reduce the amount of tracheal deviation. In the remainder, thoracoplasty was done to obliterate "dead" pleural space. All had quiescent disease at the time of thoracoplasty. There were no postoperative deaths in this group. Three of the patients are alive and well. Contralateral disease developed in one patient three years later. She had roentgenographic evidence of disease in that lung prior to the operation.

Effects of Operative Interruptions on the Results

Considerable emphasis has been placed on the importance of the degree of pulmonary collapse obtained in determining the results of thoracoplasty. Failures are customarily ascribed to ineffective collapse resulting either from interruptions in the operative schedule or from an improperly performed thoracoplasty. Inasmuch as interruptions in the proper spacing of operative stages are considered particularly serious, an analysis was made of the cases in which, for one reason or another, long intervals occurred between thoracoplasty stages. Again, attention was given to the type of pulmonary lesion involved.

Interruptions in the completion of the thoracoplasty occurred in 58 patients, in most instances as a result of wound infection or spread of the disease. Of this number, 26 had an unsatisfactory result, accounting for all but 4 of the 30 early failures. Of particular significance is the fact that 19 of the 26 failures were in Groups II to V inclusive, while only 7 were in Group I, although this group was larger than the others combined (table 2). Successful results were noted in 32 patients who had had similar interruptions. Twenty-eight of the 32 cases belonged to Group I, while only 4 belonged to Groups II to V, inclusive. In Group I (fibrocaseous tuberculosis) the disease was limited and showed a natural tendency to heal. This group was found most suitable for thoracoplasty. Interruptions in the completion of the operation were not particularly serious on the final results. However, in the remaining groups which did not respond as favorably to thoracoplasty because of rigid or tension cavities, bronchiectasis, or cavities in the paramediastinal area, delays in the staging of the operation were particularly detrimental. The type of lesion present in these groups required as complete a surgical collapse as possible to achieve a satisfactory result, which was frequently impaired by the delay between stages.

DISCUSSION

A study of the results of thoracoplasty in the various forms of pulmonary tuberculosis indicates that the nature of the tuberculous process has considerable bearing on the final outcome of the operation. Although the majority of the cases (Group I, fibrocaseous) present a type of disease which responds satisfactorily to thoracoplasty, there are a number of smaller groups in which the operation is not nearly as effective and which account for almost all the surgical failures. The poor results obtained with caseocavernous tuberculosis are obviously

a consequence of the rapidly progessive nature of the disease. There are groups in which the disease appears sufficiently stabilized to warrant surgery, but other factors inherent in the basic pathologic pattern, such as rigid cavity wall, unpredictable thin-walled cavity, tuberculosis bronchitis, associated suppurative bronchiectasis, or the presence of a markedly thickened pleura, militate against a successful thoracoplasty.

The best results with thoracoplasty are obtained in the group of unilateral active fibrocaseous tuberculosis. It is quite apparent that the ultimate statistical picture of the operation in a large series of cases depends considerably upon the size of this group. Unless the results of thoracoplasty are analyzed according to the types of disease treated, the significance of this important factor is not appreciated. In the present series the operative and late mortality rates were lower for the fibrocaseous group than for the entire series. Likewise, there were few late recurrences (tables 2, 6, and 9).

Thoracoplasty for fibroid tuberculosis is associated with a large percentage of failures. These result not only from the difficulty in effectively collapsing markedly fibrotic lesions associated with emphysema but also because of the impaired respiratory function which may accompany this type of disease. The majority of the patients with fibroid tuberculosis are over forty years of age and have been ill for many years. In the present series the operation was complicated by dyspnea and residual disease in almost 50 per cent of the patients in this group. Unusual care must therefore be exercised in selecting patients with fibroid tuberculosis for thoracoplasty.

The results of thoracoplasty in the group of large, thin-walled cavities are unpredictable. The disease became arrested in approximately 60 per cent of our patients, many of whom required extensive surgery to achieve this result. The difficulties encountered in the closure of such cavities result in great part from the presence of check-valve mechanisms in the draining bronchi. Recently, in such cases we have employed thoracoplasty from below upward with the intention of anchoring the lung below the cavity so that the latter is prevented from dropping into the thoracic cage. In a comparable number of cases, this procedure has eliminated the need for additional or supplementary operations. Of late, pulmonary resection is also being used with increasing frequency in the treatment of these patients with large, thin-walled cavities.

The treatment of fibroid tuberculosis and bronchiectasis with thoracoplasty is very disappointing. Because of the associated bronchiectasis, the operation is often complicated by retention of secretions and bronchogenic dissemination of the disease. Although sputum "conversion" occurred in some of the patients, the survivors continue to be plagued by symptoms referable to the mixed infection. Recent experience indicates that resection followed by thoracoplasty is preferable, especially in view of the added protection offered by streptomycin.

SUMMARY

An analysis has been made of the results obtained in 168 patients with pulmonary tuberculosis who were treated with extrapleural thoracoplasty. The purpose

of the study was to evaluate the factor of the type of disease under treatment in relation to the late results of the operation. None of the patients received streptomycin.

The late results for the entire series were as follows: Of 141 patients traced who had had thoracoplasty from two to six years previously, 63.1 per cent had arrested tuberculosis and 22.7 per cent active disease. The operative mortality was 5.3 per cent and the over-all mortality 14.2 per cent. All but 5 of the 168 cases had stabilized lesions at the time of surgery. Operative complications resulting in delays in the completion of the thoracoplasty were analyzed. It was found that the outcome of such delays depended to a great extent on the type of lesion.

The entire series of cases was then classified according to the type of lesion and the results of the operation compared for each group. The largest group consisted of patients with unilateral fibrocaseous tuberculosis. The best results of thoracoplasty were obtained in this group. Only one patient with an initially successful result had a "breakdown" under the thoracoplasty. It is the size of this group which determines the over-all statistical results of thoracoplasty.

Giant thin-walled cavities, thick-walled cavities, and tuberculosis with bronchiectasis accounted for most of the failures in the series. It was not the size of the cavity *per se* but the underlying pathologic pattern which influenced its closure with thoracoplasty. Currently, these types of cases are being treated preferably with resection in combination with streptomycin. It will take a number of years before it will be possible to assess the results of such treatment.

SUMARIO

Influjo de la Forma de la Enfermedad sobre el Resultado de la Toracoplastia en la Tuberculosis Pulmonar

Este análisis comprende 168 tuberculosos pulmonares tratados con la toracoplastia extrapleural, teniendo por objeto justipreciar la relación que guardaba la forma de enfermedad con los resultados tardíos de la operación. Ninguno de los enfermos recibió estreptomicina.

Los resultados tardíos para toda la serie fueron éstos: De 141 enfermos descubiertos que habían sido objeto de una toracoplastia de dos a seis años antes, 63.1 por ciento tenían tuberculosis estacionada y 22.7 por ciento activa. La mortalidad operatoria fué de 5.3 por ciento y la global de 14.2 por ciento. Todos los casos, menos 5, tenían lesiones estabilizadas en la fecha de la operación. Analizadas las complicaciones quirúrgicas que hicieron demorar la terminación de la toracoplastia, observóse que el resultado de tal demora dependía en gran parte de la forma de la lesión.

Toda la serie fué clasificada después conforme a la forma de la lesión, comparándose el resultado de la intervención en cada grupo. El grupo más numeroso constaba de enfermos con tuberculosis fibrocaseosa unilateral, y en este grupo fué que la toracoplastia obtuvo sus mejores resultados. Un solo enfermo con resultado inicial bueno experimentó una "recaída" con la toracoplastia. La

magnitud de este grupo es lo que determina el resultado estadístico global de la toracoplastia.

Las cavernas gigantes de paredes delgadas, las cavernas de paredes gruesas y la tuberculosis con bronquiectasia comprenden la mayor parte de los fracasos de la serie. No el tamaño *per se*, sino el subyacente patrón patológico de la caverna fué lo que afectó el cierre de la misma con la toracoplastia. Actualmente, esos casos son tratados de preferencia con la resección combinada con la estreptomicina, mas tardarán varios años antes de que sea posible valorar el resultado de ese tratamiento.

PLEURAL DECORTICATION IN PULMONARY TUBERCULOSIS[1,2,3]

JOSEPH WEINBERG AND J. DWIGHT DAVIS

(Received for publication May 5, 1949)

INTRODUCTION

The problem of tuberculous empyema and its precursor, the unexpandable lung following pneumothorax, has long been a disturbing one. Woodruff (1) in a review of 135 cases found that 28 per cent of the pure tuberculous empyemas and 60 per cent of the patients with mixed infection died within five years. In more than half of the fatalities the disease was minimal in the opposite lung, indicating that the tuberculous pleuritis was an important, if not the principal, factor in causing death. Of those surviving more than five years, over half remained under treatment.

Stimulated by the excellent results obtained with decortication in hemothorax during World War II (2, 3), a number of surgeons have extended the procedure to tuberculous empyema in its established and incipient forms (4, 5, 6, 7, 8, 9, 10). There are now enough cases reported to indicate that the procedure may be successfully applied in tuberculosis as far as obliterating the abnormal pleural space and re-expanding the lung are concerned. In the few years that have elapsed since adoption of the procedure, it appears that two of the feared complications, dissemination of the tuberculous process and development of tuberculous sinuses in the surgical wounds, are infrequent occurrences. This is largely credited to the use of streptomycin during the surgical period.

OBSERVATIONS

Indications for Decortication

We consider three classes of cases to be suitable for decortication: the frank empyema, the persistent abnormal space with thickened membrane and without suppuration, and the abnormal space which tends to become obliterated by extreme shifting of the mediastinum and overexpansion of the opposite lung.

Obliteration of the abnormal space and re-expansion of the lung is most easily accomplished in the nonsuppurative cases in which decortication is performed as soon as it is determined that satisfactory re-expansion of the lung cannot be accomplished by nonsurgical means. Satisfactory expansion by nonsurgical means implies that the lung will expand progressively to fill the space without extreme shifting of the mediastinum or overinflation of the opposite lung.

[1] From the Departments of Thoracic Surgery and Thoracic Medicine, Birmingham Veterans Administration Hospital, Van Nuys, California.

[2] Presented before the Medical Section, as part of the symposium on *Surgery*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 5, 1949.

[3] Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by th authors.

Decortication is relatively difficult in the frank tuberculous empyemas of either the mixed or unmixed type, sharp dissection being required for much of the separation. Complete re-expansion of the lung is not always obtained, and all of our surgical complications have occurred in this group. This has made us appreciate the importance of anticipating established frank empyemas and performing decortication before extreme fibrosis occurs.

The degree of activity of the tuberculosis in the underlying lung plays an important part in deciding whether or not decortication should be performed. If acute tuberculous pneumonitis is present, one should wait until the process has subsided before considering decortication. In those cases in which there is extensive fibrosis, one may wish to obliterate the empyema, even though re-expansion of the lung following decortication is improbable. In these cases, we have followed decortication with thoracoplasty. The thoracoplasty need not be of the conventional type with removal of transverse processes and the first rib, since its only purpose is to obliterate the space left by the incompletely expanded lung.

TABLE 1

Precursor of Pleural Membrane

Induced pneumothorax	8 cases
Spontaneous effusion	1 case
Induced followed by spontaneous pneumothorax	1 case
Pneumothorax and pneumonolysis	5 cases

If the thoracoplasty is for the purpose of compressing a pulmonary lesion, however, it is performed according to accepted procedure.

If bronchoscopy reveals a fibrous stenosis of a major bronchus or if bronchopleural fistulae are present which probably cannot be closed satisfactorily, the involved lung or segment of lung should be resected at the time of decortication.

It is preferred that the patient have had no previous courses of streptomycin treatment which would cause the microorganisms to be drug-resistant at the time of operation. Experience with streptomycin in decortication and in other surgical procedures indicates that local activation of the disease and spread to other parts of the lungs is apt to occur if streptomycin is not used or if streptomycin has been given previously.

Etiology

Pneumothorax, either induced or spontaneous, was the precursor of the tuberculous pleuritis in all but one of our cases (table 1). The exception was a case of spontaneous empyema classified as tuberculous by history, but not proved. In 5 of the 15 patients, pneumonolysis had been performed subsequent to pneumothorax and the sequence of events indicates that the complication of fixed abnormal space with thickened membrane and pleural effusion was a result of the pneumonolysis.

Pathology

In the very earliest stage of development of the pleural membrane there is an opacification of the pleura without gross evidence of a membrane. Microscopic

examination of the pleura at this stage shows a thin fibrino-fibrous membrane moderately infiltrated with leukocytes and histiocytes and richly vascularized. This is a reversible phase in which re-expansion can probably be obtained by nonsurgical means. (Observation based on specimen obtained from a pneumothorax case at the time of lobectomy.)

The next stage of progression is represented by a grossly recognizable membrane with the visceral portion 2 or 3 mm. in thickness and the parietal portion

FIG. 1. G. E. (Case 12). Nonsuppurating membranous sac removed to obliterate abnormal space and permit re-expansion of lung.

varying from 3 to 7 or 8 mm. in thickness (figure 1). he membrane has a hyalinized fibrous middle layer and markedly vascular attached and peripheral layers. Typical tuberculous lesions are usually evident in all of the layers. The fluid in the pleural space is clear or moderately turbid, and may be positive for *M. tuberculosis*. The pleural endothelial layer may still be recognized. In this stage the process may be considered irreversible if nonsurgical means fail to produce re-expansion of the lung after a trial of several months.

The frank empyema presents a greatly thickened and roughened pleural membrane with purulent fluid within the sac (figures 2 and 3). Usually all vestiges of the endothelial layer are lost, and the fibrotic process extends into the substance

of the pleura and even into the lung. The middle hyalinized layer may show any or all stages of inflammation and degeneration, from areas of localized acute abscesses to areas of calcification. Tuberculous lesions may be present with or without caseation. The ribs show degenerative changes and tend to assume a triangular form in cross section.

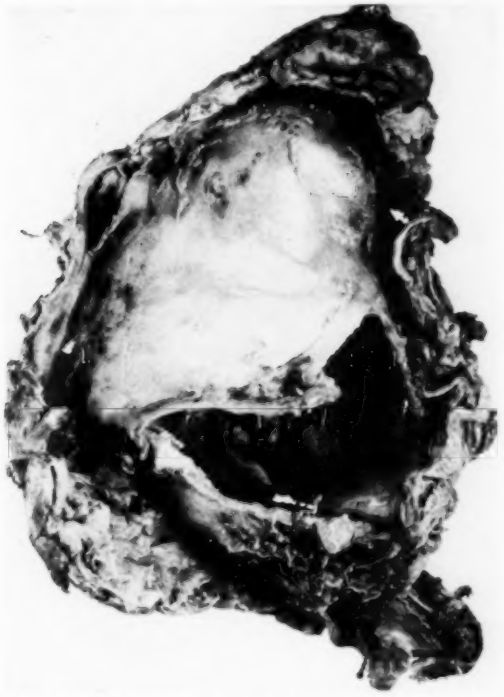


FIG. 2. R. P. (Case 9). Moderately severe tuberculous empyema. Note "roughened" lining in contrast to smooth lining in figure 1. Thickened peripheral ring marks the junction of the visceral and parietal portions of the membrane.

In addition to the alterations of the pleura, the underlying lung may be folded into bizarre patterns, with areas of atelectasis presumably resulting from the distortion induced by the constricting membrane. These findings are emphasized because it is thought by some that the restriction of the lung induced by the membrane is a favorable situation even though the abnormal pleural space is undesirable. In several of our cases large segments of folded lung have been observed, with atelectasis distal to the resultant bronchial obstruction.

RESULTS

Fifteen operations of decortication have been performed on patients in whom active tuberculosis of the lung had been diagnosed at some period during the

illness and in whom a thickened membrane had existed for periods ranging from several months to more than twenty years. At present eighteen months have elapsed since the first operation and four months since the latest operation. There have been no deaths and the abnormal space has been obliterated in all

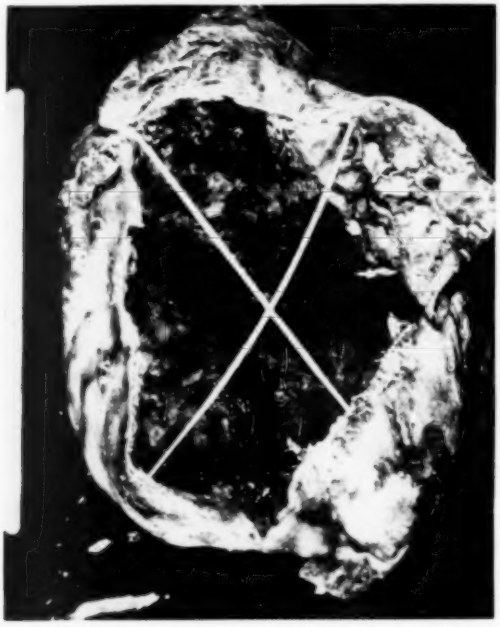


FIG. 3. A. R. (Case 15). Old empyema sac of more than 20 years' duration. Note shaggy lining. Sharp dissection required for most of its separation from the lung.

TABLE 2

Unsuccessful Therapy for Obliteration of Space before Decortication

Abandonment of pneumothorax with or without aspiration	9 cases
Streptomycin intrapleurally (0.2 Gm. 3 times weekly over 86 day period)	1 case
Thoracoplasty (resulted in draining sinus)	1 case
Phrenic paralysis	3 cases

except one of the cases. The single failure is in a patient who had been previously treated with streptomycin. In two instances, thoracoplasty was added to complete the obliteration of the space. These were cases of frank empyema.

Obliteration of the abnormal pleural space had been attempted in all of the cases prior to performing the decortication (table 2). Nine of the 15 patients had been treated by abandonment of the pneumothorax with or without aspiration

of fluid. One patient was treated with aspirations followed by intrapleural injections of 0.2 Gm. of streptomycin three times a week for eighty-six days. A thoracoplasty with the removal of a major portion of eleven ribs not only failed to obliterate the empyema in one of this series, but resulted in a draining tuberculous sinus which did not heal until the empyema sac was removed by decortication (case 8).

Five of the cases in the series were classified as frank tuberculous empyemas and 3 were classified as empyemas complicating pulmonary tuberculosis with no histologic or bacteriologic evidence of active tuberculous infection at the time of decortication (table 3). The empyemas have been eradicated in all except the patient who had received a previous course of streptomycin therapy. In 2 of the cases, stationary active disease was present in the contralateral lung at the time of decortication. In neither case has any evidence appeared of spread of the pulmonary tuberculosis following surgery. In 2 of the empyema cases, thoracoplasty was performed to complete the obliteration of the space (table 4). This was done at the time of decortication in one case, and three weeks after decortication in the other. In one patient, phrenic paralysis was performed one week

TABLE 3

Types of Cases Decorticated

Unexpanded lung with clear fluid	7 cases
Undrained empyema	7 cases
Draining empyema	1 case

11 of the membranes showed histologic evidence of tuberculosis.

after decortication to obliterate a small persistent space. Thoracoplasty was performed to compress underlying pulmonary lesions in 2 cases. In one instance, thoracoplasty has been advised to compress a pulmonary lesion but has not yet been accepted by the patient.

Seven cases were classified as unexpanded lung without evidence of suppuration. All of these had been treated by medical means for at least three months in an attempt to obliterate the space. In one instance the decortication was performed to arrest extreme mediastinal shift and overexpansion of the contralateral lung. Eradication of the space with complete re-expansion of the lung has been obtained in all of these cases without the addition of other surgical procedures.

Measurements of pulmonary function before and after decortication have been made by indirect methods which reflect the degree of altered function. Vital capacity, breath-holding time, and inspiratory and expiratory films indicate that an appreciable increase in function has been obtained. In general, the total pulmonary function is decreased in the first month but is increased over the preoperative level after three months (table 5).

Surgical Procedure

The preparation for surgery and the operative technique used in these cases has been previously discussed by us (6, 7) and only a brief description will be given here. Strepto-

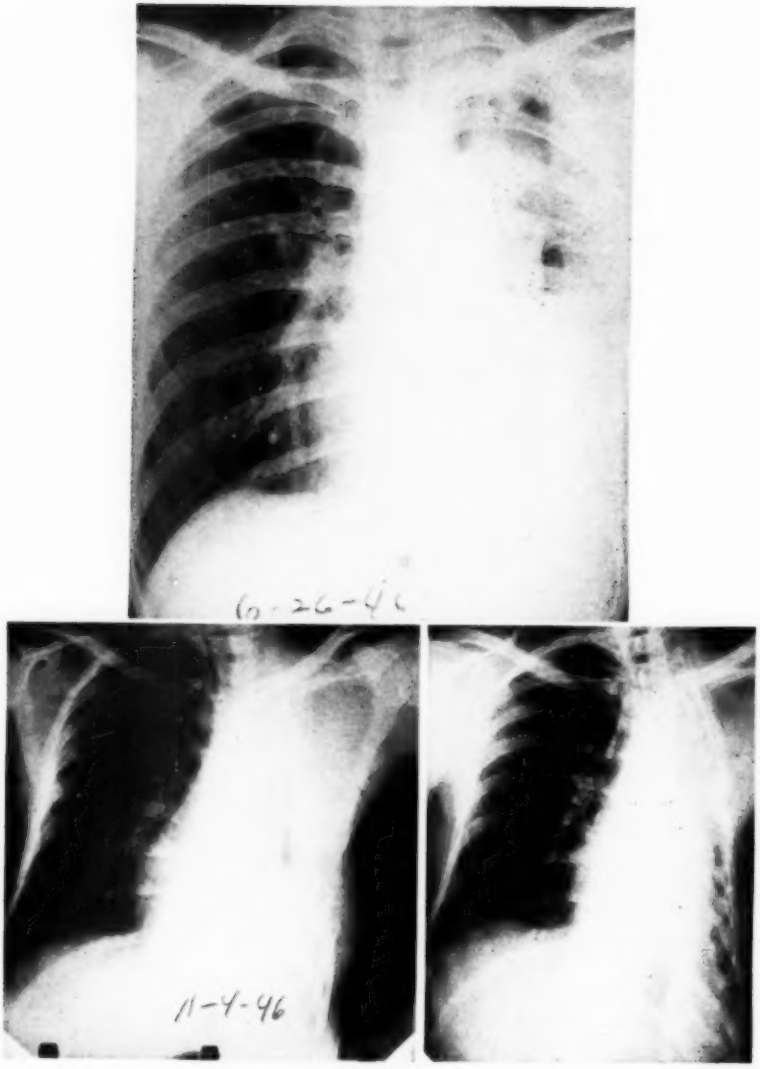


FIG. 4. F. S. (Case 8). This series illustrates a case in which thoracoplasty not only failed to obliterate the tuberculous empyema, but resulted in a tuberculous sinus of the thoracic wall. Subsequent decortication under streptomycin coverage obliterated the empyema and eradicated the sinus.

a. (Upper) Before thoracoplasty.

b. (Lower left) After thoracoplasty and before decortication.

c. (Lower right) After decortication.

mycin, 1.0 Gm. daily intramuscularly, is started five to seven days before operation; and penicillin, 200,000 units daily intramuscularly, is started three days before operation. At

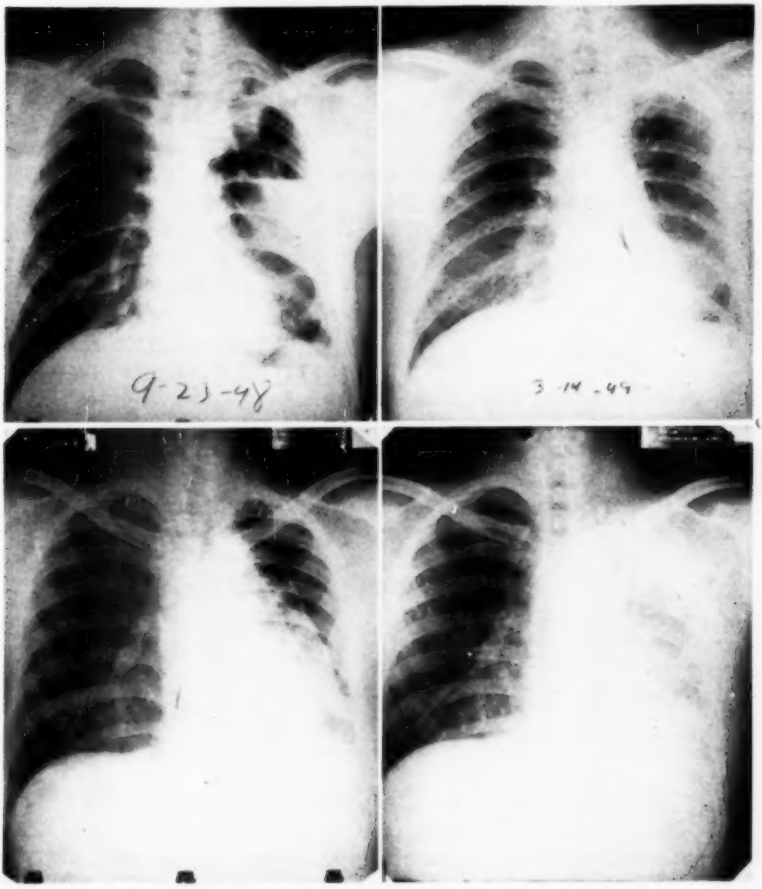


FIG. 5. W. T. (Case 13).

a. (Upper left) Tuberculous empyema before decortication.

b. (Upper right) Nine weeks after decortication. Lung has expanded and empyema has been obliterated without deformity of thoracic wall.

FIG. 6. J. S. (Case 11).

a. (Lower left) Before decortication.

b. (Lower right) Four weeks after decortication. Thoracoplasty performed three weeks after decortication to compress a left apical pulmonary lesion.

the present time a closed system of ether anesthesia is used with an endotracheal catheter. The patient is placed in a near supine position with the affected side slightly elevated to

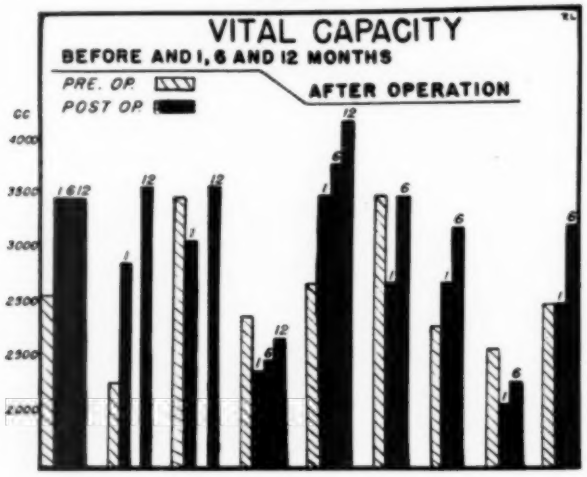
permit extension of the thoracic incision to the posterior axillary line. An intercostal incision is made, preferably in the fifth interspace, and exposure is obtained by means of a Finochietto rib spreader. No ribs are removed or divided. The membrane is separated from the costal wall and visceral surfaces, and also from the diaphragmatic surface if a cleavage plane is readily developed. The membrane is preferably removed in one piece as this facilitates the maintenance of the cleavage plane and thus minimizes trauma to the lung. Drainage

TABLE 4

Additional Surgery following Decortication

Thoracoplasty:	
To complete obliteration of abnormal space	2 cases
To compress underlying pulmonary lesions	2 cases
Phrenic paralysis:	
To complete obliteration of abnormal space	1 case

TABLE 5



catheters are inserted anteriorly and posterolaterally through separate stab wounds before closing the surgical incision, and these are later connected with a mild suction apparatus. The tubes are removed within several days following operation.

Surgical Complications

In one instance several hundred cubic centimeters of fluid containing *M. tuberculosis* were evacuated spontaneously through the surgical wound one month after decortication. This patient had received a course of streptomycin therapy prior to consideration of decortication, and it is probable that his organisms were resistant to streptomycin at the time of surgery. The sinus, which formed at the site of evacuation of the fluid, became closed in six weeks. Thoracoplasty has been advised to complete the obiteration of the persistent pleural space, but

has not yet been accepted. The patient is classified as a failure at the time of the preparation of this report, but it is too early to predict the final result. It is significant that this was the only case in which a course of streptomycin therapy had been given some time prior to surgery.

The only serious surgical complication was in a patient whose empyema had existed for more than twenty years. In this case a portion of the diaphragm was removed with the membrane, due to obscuration of the field by excessive bleeding. He now has a moderate herniation of the stomach into the thorax, but his recovery has been uneventful otherwise. He has no symptoms referable to the herniation. This experience has made us realize the danger of decorticating the diaphragm in long standing cases of frank empyema, and we would advise against the removal of this portion of the membrane if separation cannot be obtained easily by blunt dissection.

There have been three instances of fracture of a rib due to pressure of the retractor blades. In none of these instances did the patient complain of intercostal pain following surgery.

One case with postoperative leakage of air from the pulmonary surface required reopening of the surgical wound nine days after decortication because of failure of the lung to expand. At reoperation the leak was sealed with "fibrin foam" held in place with fine cotton sutures. Following this the patient made a very satisfactory recovery with complete obliteration of the pleural space. This case was described in an earlier report (6).

CASE REPORTS

The first 7 of the 15 cases comprising this study have been reported in earlier articles (6, 7).

Case 8: F. S., male, age 25, was diagnosed pulmonary tuberculosis, far advanced, left, in January 1946. Pneumothorax, left, was started at that time and was discontinued in March 1946. Turbid green fluid was aspirated on several occasions between July 12 and August 16, 1946.

On admission to Birmingham Veterans Administration Hospital he showed a left hydropneumothorax, with adhesions between the apex of the lung and the thoracic wall and with several cavities in the left upper lobe. The fluid was positive for *M. tuberculosis*. An eleven-rib thoracoplasty was performed in four stages between August and November, 1946. The patient left the hospital in February 1947 against medical advice. He returned in September 1947 because of a draining sinus in the lower part of the thoracic wall which communicated with a tuberculous pleural empyema. Bronchoscopy at this time showed no evidence of bronchial obstruction. Decortication was decided on, and the patient was prepared for surgery. The preoperative preparation included the administration of streptomycin, 1.0 Gm. daily intramuscularly, beginning October 31, 1947.

Operation was performed on November 13, 1947. A lateral thoracic incision was made over the tenth rib and a portion of necrotic rib was removed. The pleural empyema space, which extended from the diaphragm upward for 8 cm., was resected except for a small area near the apex. A catheter drain was placed through a separate stab wound and was connected with a suction apparatus. One Gm. of streptomycin and 200,000 units of penicillin were dissolved in distilled water and instilled into the pleural space. The thoracic wall incision was closed in layers with interrupted cotton sutures.

The surgical wound healed primarily. Penicillin therapy was discontinued four days after operation and streptomycin therapy was discontinued sixty days after operation. Phrenic nerve crush was performed November 24, nine days after operation, because of a questionable pleural space. Planigrams made subsequently showed complete obliteration of the space. *M tuberculosis* could not be demonstrated in the fluid at the time of operation, but microscopic examination of sections of the membrane showed typical tubercles with caseation and epithelioid cells. The patient left the hospital against medical advice three and one-half months after decortication. At that time the sputum was "converted" and there was no evidence of residual empyema. Indirect reports indicate that his course has been favorable up to the present time (figure 4).

Comment: This patient is an example of chronic tuberculous empyema in which extensive thoracoplasty failed to obliterate the space and resulted in a draining sinus through the thoracic wall.

In the light of experience, the phrenic paralysis which was induced nine days after operation was probably unnecessary and we do not recommend it as a routine procedure following decortication.

Case 9: R. P., male, age 26, was diagnosed as having pulmonary tuberculosis in August 1947. The disease was unilateral with cavitation in the left apex. Pneumothorax was started November 21, 1947 and apical pneumonolysis was performed in February 1948. Fluid, which developed following severance of adhesions, was positive for *M. tuberculosis*. The pneumothorax was abandoned August 4, 1948 because of persistent fluid and formation of a pleural membrane. His last sputum culture positive for *M. tuberculosis* was obtained on March 29, 1948. Roentgenographic examination on July 9, 1948 showed a cavity in the left apical region, mediastinal shift to the left, narrowing of the interspaces, thickening of the pleura, and fluid in the pleural space.

Decortication was performed August 13, 1948 after one week of streptomycin, 1.0 Gm. daily intramuscularly. The parietal membrane, 0.5 to 1.0 cm. in thickness, was separated by finger and gauze dissection. The visceral membrane, 0.3 cm. in thickness, was separated by blunt and sharp dissection except for a small adherent patch which was left on the lingula. The membranous sac had a capacity of approximately 700 cc. and presented a granular inner surface (figure 2). It showed typical tubercles histologically. Drainage tubes were inserted in the usual manner.

His postoperative course was uneventful. The tubes were removed on the fourth day. The lung has remained fully expanded since then. Streptomycin was continued for a full forty-two day course because at the time of surgery nodes which were possibly the site of active tuberculosis were palpated in the lung.

The vital capacity, which was 2,300 cc. before operation, was 2,700 cc. one month after operation and 3,200 cc. six months later.

Case 10: W. L., male, age 48, was diagnosed as having pulmonary tuberculosis in 1926. A right pneumothorax was started that year and was continued for seven and one-half years. A pleural effusion which developed was aspirated at various times in the following years. His last sputum positive for *M. tuberculosis* was obtained in 1938.

Shortly after his admission to this hospital, 175 cc. of turbid purulent fluid were aspirated from the right pleural space. At this time his chief symptoms were weakness and fatigue. There was no evidence of active pulmonary tuberculosis. Roentgenographic examination showed opacification limited to the lateral half of the right thorax.

Streptomycin, 1.0 Gm. daily intramuscularly, was started one week before decortication. At surgery the ribs were overlapped, thickened, and markedly degenerated. Two ribs were fractured by the rib spreader in exposing the pleura. The membrane was separated by blunt and sharp dissection from the parietal and visceral surfaces, not including the diaphrag-

matic surface. The membrane measured up to 2.0 cm. in thickness in some areas. Very little expansion of the lung was obtained and portions of four ribs were resected to complete the obliteration of the space. Postoperative recovery was uneventful. The space remains obliterated several months after operation.

Cultures and histologic examination of the membrane were negative for tuberculosis. It was markedly hyalinized throughout and was calcified in many areas. The vital capacity which was 2,100 cc. before operation had dropped to 1,600 cc. one month after operation. The breath-holding time remained constant. Further determinations of function have not yet been made.

Comment: This empyema is representative of the type which may persist for years with only mild general symptoms but which is a continuing source of systemic infection. At the time the patient was seen by us, thoracoplasty would not have obliterated the hard-shelled space and a Schede operation would have been the only alternative surgical procedure.

Case 11: J. S., male, age 25, was first found to have pulmonary tuberculosis in June 1945. A left pneumothorax was induced in July 1945 because of an apical cavity. Pneumonolysis, performed October 10, 1945, resulted in a persistent pleural fluid accumulation. Temporary phrenic paralysis was induced November 5, 1946. The pneumothorax was abandoned July 6, 1948 because of thickening of the pleura which probably had its inception in December 1945. Bronchoscopy at this time showed no evidence of bronchial occlusion.

A left pleural decortication was performed August 25, 1948 after the usual preparation, including streptomycin intramuscularly. A thick-walled empyema sac of 700 cc. capacity and containing fibrino-purulent material was removed, mostly by gauze and finger dissection. Some sharp dissection was required over the pulmonary surface and several pulmonary air leaks were sealed with "fibrin foam." The distal half of the lingula was amputated because of a large soft caseated abscess in its tip.

The postoperative course was without complications. A left four-rib thoracoplasty was performed three weeks later to compress an apical lesion (figure 6).

The vital capacity and breath-holding time, which were 3,200 cc. and 32 seconds, respectively, before operation, were 2,300 cc. and 28 seconds one month after operation. Later determinations have not yet been made.

A full forty-two day course of streptomycin was given to this patient.

Case 12: G. E., male, age 26, was found to have left subapical tuberculosis in December 1945. Left pneumothorax was started in April 1946 and continued for two years.

At the time of admission to Birmingham Veterans Administration Hospital there was thickening of the pleura with fixation of the lung, fluid, mediastinal shifting to the affected side, and narrowing of the intercostal spaces. Bronchoscopy showed evidence of tracheal shift.

Decortication was performed September 10, following the usual preliminary examination and preparation. Separation of the total membrane was accomplished without difficulty. The membranous sac had a capacity of about 800 cc. (figure 1). A caseous area was uncovered just below the apex. Its contents were evacuated and the space filled with "fibrin foam" to seal an air leak.

The postoperative course was without untoward incident. Streptomycin was continued to complete a forty-two day course of 1.0 Gm. daily intramuscularly.

The vital capacity and breath-holding time, which were 2,800 cc. and 30 seconds before operation, were 3,500 cc. and 55 seconds six months after operation.

Case 13: W. T., male, age 28, was found to have far advanced pulmonary tuberculosis on the left in April 1947. Pneumothorax was started in May 1947. Fluid formed in April 1948

and aspirations of fluid were performed at intervals of a few months. The pneumothorax was abandoned in September 1948 because of increasing fluid. He entered this hospital a few weeks later with evidence of thickened pleural membrane, fixed lung, and shift of the mediastinum to the affected side. A moderate hydropneumothorax was present. Bronchoscopy was negative except for evidence of a shift of the trachea to the left.

A left decortication was performed January 5, 1949 after one week of streptomycin therapy. Separation of the sac in one piece was accomplished without difficulty. The sac was lined with a shaggy fibrino-purulent membrane and had a capacity of about 500 cc.

The postoperative course was without complications. Streptomycin, 1.0 Gm. intramuscularly daily, was continued to complete a forty-two day course of treatment of the pulmonary disease.

The vital capacity and breath holding time, which were 3,500 cc. and 35 seconds before surgery, measured 3,000 cc. and 40 seconds one month after surgery. Subsequent measurements have not yet been made.

Case 14: L. B., male, age 38, was found to have far advanced, bilateral, severe pulmonary tuberculosis in October 1945. A right pneumothorax was started in January 1946 and was discontinued at the time of admission to Birmingham Veterans Administration Hospital in September 1948 because of a mixed pleural infection. At this time there was almost complete obscuration of the right lung and evidence of exudative disease in the left midlung field. The sputum was positive for *M. tuberculosis*. Bronchoscopy revealed a moderate hyperemia of the left upper lobe bronchus and a shifting of the trachea to the right.

The patient had received a forty-two day course of streptomycin treatment beginning November 22 and ending December 2, 1948. This included 1.0 Gm. daily intramuscularly and 0.2 Gm. intrapleurally three times a week. The left pulmonary lesion regressed under this therapy, but the condition of the right pleural empyema remained unchanged.

Decortication was performed January 6, 1949 after resuming streptomycin therapy one week earlier. The membrane was removed as an intact shell. Sharp dissection was required over most of the pulmonary and diaphragmatic surfaces. The empyema sac contained a greenish gray fibrino-purulent exudate. The lung was fully expanded at the time of closure of the surgical wound.

There was evidence of a pleural effusion one week after operation, but it could not be located with an aspiration needle. One month after surgery several hundred cubic centimeters of clear fluid were evacuated spontaneously through the surgical wound. The fluid was postive for *M. tuberculosis* by culture. The sinus formed by the escaping fluid became closed six weeks later. However, the space occupied by the fluid has not been obliterated. Thoracoplasty has been advised, but the patient has left the hospital to attend to personal problems not directly related to his illness. This was against the advice of his physicians.

Comment: This patient must be counted as a failure at the time of this report. However, if thoracoplasty is performed in the near future, obliteration of the space may yet be accomplished.

This case presents indirect evidence of the hazard of performing decortication if the patient has had a previous course of streptomycin therapy with probable resulting loss of therapeutic effect on the microorganisms.

Case 15: A. R., male, age 51, was first discovered to have tuberculosis in 1918. The basis for the diagnosis is not known to us. He was given bed rest therapy from 1918 to 1920. During that period he developed a left pleural effusion which was aspirated on numerous occasions for several years. He experienced moderate dyspnea and weakness in the years following, but was able to carry on regular activities.

In October 1947 the symptoms of dyspnea and weakness became pronounced. Repeated aspirations of the left pleural space showed a turbid fluid, negative for *M. tuberculosis* and other pyogenic organisms.

He was admitted to Birmingham Veterans Administration Hospital October 16, 1948. Examination revealed a fixed left lung with greatly thickened pleural membrane and turbid fluid in the left pleural space. There was an extreme narrowing of the intercostal spaces and the mediastinum was displaced to the affected side. A diagnosis of chronic empyema was made, with probable spontaneous onset some time within several years following the year 1918.

Inasmuch as the pyothorax was increasing in severity, as indicated by the increase in the severity of symptoms and the physical signs, decortication was decided upon.

Streptomycin, 1.0 Gm. daily intramuscularly, was started January 22, 1949. Penicillin, 300,000 units daily, was started January 24.

Decortication was performed January 26. An incision was made in the left fifth interspace from the parasternal line to the posterior axillary line. Removal of the membrane from the costal surface was performed by blunt dissection, but against much greater resistance than in previous cases. Separation of the membrane from the pleural surface was almost entirely by sharp dissection. Although large areas of pulmonary parenchyma were exposed, air leakage was minimal and had practically subsided at the time of completion of the operation. In separating the membrane from the diaphragmatic surface, an area of several square centimeters of the membranous portion of the left hemidiaphragm was removed with the empyema sac. This was due to firm fibrotic adherence of the membrane to the diaphragm and to obscuration of the field by bleeding which was more than that usually encountered. Because this operation was associated with excessive trauma and bleeding and had consumed more time than previous operations, it was decided not to attempt closure of the defect in the diaphragm. Four liters of blood were given intravenously during the decortication. The lung had not fully expanded to fill the pleural space at the end of the operation, because of pulmonary fibrosis.

The patient's course was very satisfactory following surgery, notwithstanding a moderate herniation of the stomach into the pleural space. The pleural space was reduced to a pocket of several cubic centimeters at the time of preparation of this report. Postoperative determinations of the vital capacity and breath-holding time have not yet been made.

Comment: It is assumed that this long standing chronic empyema was of tuberculous origin, probably the result of a spontaneous tuberculous pleural effusion. This case is an example of acute exacerbation of inflammation in an empyema that had been dormant for many years.

The difficulty encountered in separating the membrane from the diaphragm has made us wary of attempting to include this portion of the membrane in the decortication in cases in which there is firm fibrotic adherence between the membrane and the diaphragm.

SUMMARY

Fifteen patients with unexpandable lung and persistent pleural space following unsuccessful pneumothorax have been treated by total or almost total decortication of the pleural membrane. The cases include various degrees of thickened pleural membrane, from simple thickening with clear fluid accumulation to frank draining empyema.

There have been no deaths, and the few surgical complications have not interfered with eradication of the abnormal pleural space.

In 2 cases with frank empyema, the lung did not expand completely and it was necessary to add limited thoracoplasty to accomplish obliteration of the space. In 2 others, thoracoplasty was added to compress underlying pulmonary lesions. In another, the only case which may be considered a possible failure, thoraco-

plasty has been advised to complete the obliteration of a persistent space but has not yet been accepted by the patient.

Indirect measurements indicate that there is an immediate postoperative decrease in total pulmonary function, with an appreciable increase in function after several months. In most of the cases, the eventual function is beyond that estimated immediately before operation.

Streptomycin, 1.0 Gm. daily, was used during the surgical period, beginning several days before operation and continuing for two to five weeks after operation, depending upon the degree of pulmonary pathology. In the only case in which a course of streptomycin therapy had been given prior to decortication, a pleural effusion containing *M. tuberculosis* developed one month after decortication. This is the possible failure mentioned above.

Decortication is performed more easily and with less danger of surgical complications in those cases which have not reached the stage of frank empyema. For this reason we believe that the operation should be performed as soon as it is decided that medical treatment will not satisfactorily obliterate the abnormal pleural space.

It is now more than eighteen months since our first operations were performed. There has been no evidence of spread of pulmonary tuberculosis and there has been only one case in which tuberculosis of the pleura was possibly activated by the decortication, the case in which streptomycin therapy had been given previously with probable loss of sensitivity.

SUMARIO

La Decorticación Pleural en la Tuberculosis Pulmonar

A 15 enfermos con pulmones inexpansibles y persistente espacio pleural a continuación de un neumotórax fracasado, se les trató con la decorticación total o casi total de la membrana pleural. Los casos comprenden varioa grados de espesamiento de la membrana pleural, variando de mero espesamiento con acumulación de líquido diáfano a franco empiema supurante.

No ha habido mortalidad, y las pocas complicaciones quirúrgicas no han vedado la erradicación del espacio pleural anómalo.

En 2 casos con empiema declarado, el pulmón no se expandió completamente y fué necesario agregar una toracoplastia limitada para conseguir la obliteración del espacio. En otros 2, se agregó la toracoplastia para comprimir lesiones pulmonares subyacentes. En otro caso, el único que puede considerarse como posible fracaso, se ha aconsejado la toracoplastia para completar la obliteración de un espacio persistente, pero el enfermo no la ha aceptado.

Mediciones indirectas indican que se presenta una disminución postoperatoria inmediata de la función pulmonar total, con aumento apreciable al cabo de varios meses. En la mayor parte de los casos, la función definitiva es superior a la estimada antes de la operación.

Durante el período quirúrgico, se empleó estreptomicina, 1.0 gm. diario, comenzando varios días antes de la intervención y continuando hasta dos a cinco semanas después, de acuerdo con la patología pulmonar presente. En el único

caso en que se había dado una serie de estreptomicinoterapia antes de la decorticación, se presentó un derrame pleural que contenía *M. tuberculosis*, un mes después de la decorticación. Este es el posible fracaso mencionado más arriba.

La decorticación se ejecuta con mayor facilidad y menos peligro de complicaciones quirúrgicas en los casos que no han llegado a la etapa de empiema declarado, por cuya razón debe realizarse apenas se decida que el tratamiento médico no obliterará a satisfacción el espacio pleural anormal.

Han transcurrido más de dieciocho meses desde que se verificaron las primeras operaciones. No ha habido signos de difusión de la tuberculosis pulmonar y sólo existe un caso en el que la tuberculosis pleural fué posiblemente activada por la decorticación: aquél en se había administrado antes estreptomicina con probable pérdida de la sensibilidad.

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Discussion of Paper by Doctors Weinberg and Davis

Dr. Victor H. Kaunitz, Mt. Morris, N. Y.: I should like briefly to present two cases which illustrate some of the points made by Doctor Weinberg. Artificial pneumothorax is designed as a temporary collapse procedure but, unfortunately, at times, it becomes permanent because of the thickened fibrous membrane formed over the lung, parietal pleura, and diaphragm. In performing a decortication, the surgeon is attempting to carry out the plan the medical man had at the start of treatment, namely, to return the collapsed lung to as near normal function as possible. Although, as has been mentioned, the amount of function restored depends to a large extent upon the amount of disease previously present in the lung, it would seem that greater function would be regained if both the diaphragmatic and parietal surfaces were decorticated, as well as the visceral pleural surface.

The first case is that of a 30 year old white male whose tuberculosis was discovered while in the service, in April 1945. A left pneumothorax was begun in May 1945, for cavity in the superior segment, left lower lobe. A left pneumonolysis was performed in July 1945. Fluid in varying amounts was present in the left pleural cavity and was always negative for acid-fast bacilli. Sputum was converted, and the pneumothorax was maintained for three and

a half years. Re-expansion was attempted late in 1948, but was unsuccessful. The patient was dyspneic on moderate physical activity. The left chest was motionless on deep inspiration, as was the left diaphragm. A left decortication was done March 10, 1949, with removal of the complete fibrous envelope in one piece. The postoperative course was uncomplicated, and four weeks after operation there is motion of the left chest wall and diaphragm. This operation was not difficult technically and total blood loss, measured by the weighed sponge technique, was 600 cc.

In cases with considerable active tuberculosis still present in the collapsed lung, or with stenosis of the main or lobar bronchi, decortication may be combined with resection and thoracoplasty. This combination of procedures is also applicable to tuberculous empyema.

The second case was that of a 32 year old white female who was admitted to the hospital in 1937 with left lower lobe cavity. Left temporary phrenic, repeated twice, was ineffective in producing cavity closure, and pneumothorax was started in May 1939. Ulceration of the left main bronchus was observed in 1941. This progressed to partial stenosis. Pneumothorax was maintained, and sputum was intermittently positive for tubercle bacilli. Tuberculous empyema developed in 1945, with fluid remaining positive, and with the lung about 50 per cent collapsed, despite repeated aspirations and attempts to re-expand it. Because of the partial stenosis and the positive sputum, excision of the empyema sac combined with pneumonectomy was decided on as the procedure of choice. This was done on February 1, 1949. Thoracoplasty through the eighth rib was done seven weeks later, to partially obliterate the left pleural cavity. The wounds healed by primary union, and postoperative courses were uncomplicated.

TUBERCULOSIS IN NURSES: CLINICAL OBSERVATIONS ON ITS PATHOGENESIS AS SEEN IN A FIFTEEN YEAR FOLLOW-UP OF 745 NURSES[1, 2, 3]

THEODORE L. BADGER AND L. FRED AYVAZIAN

(Received for publication July 13, 1948)

INTRODUCTION

During the past twenty years various concepts about the course and prognosis of tuberculosis in nurses have been presented. This study presents the clinical aspects of the pathogenesis of tuberculosis as a first or primary infection in nurses, whether it occurred in those who entered training as reactors or nonreactors to tuberculin. The report concludes a series of observations by one of the writers (1, 2, 3) on a group of nurses who entered training during the period February 1932 to February 1943, inclusive.

PLAN OF STUDY

There is nothing new in the execution of this study except the long duration of the follow-up observations. The general procedure was similar to that used in investigations in this country by Amberson and Riggins (4), Shipman and Davis (5), Geer (6), and Myers (7), and to the studies in Norway by Heimbeck (8).

All nurses were examined clinically and roentgenographically and were tested with Saranac Old Tuberculin on entrance to training. None with tuberculous lesions were admitted to training. Tuberculin tests and roentgenographic examinations of the lungs were carried out at six month intervals, although a number of nurses were unable to follow the routine because of affiliations in other hospitals or the interference of night duty.

All nurses were originally admitted as regular students to training school at the Boston City Hospital for a three year course. There has been no tuberculosis section in the hospital itself during the entire period of this study and cases of tuberculosis were scattered throughout the medical wards. Usually all tuberculous patients were segregated on the porches, but in some wards this was not possible. In 1937 one of the writers (T. L. B. (1)) recorded that there were approximately 12,300 hospital days of open pulmonary tuberculosis a year per thousand hospital beds, while patients awaited transfer to sanatoriums. In the last year of this

[1] From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

[2] Presented in part before the Medical Section, as part of the symposium on *Research and Therapy*, at the 44th annual meeting of the National Tuberculosis Association, New York, New York, June 17, 1948.

[3] This study was made possible through a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, medical section of the National Tuberculosis Association.

study there were approximately 12,000 hospital days of pulmonary tuberculosis in the hospital. All nurses, however, had one month of student training at the Sanatorium Division of Tuberculosis for the City of Boston. No *strict* "contagious technique" was established in either the hospital or the sanatorium. The nurses were instructed in the necessity of frequent hand washing as a most essential precaution, in addition to the thin mask and gown that was worn.

Nature of follow-up:

The follow-up study was carried out on a group of nurses whom the war had scattered and marriage had taken to distant parts of the country. Questionnaires, which were the initial contact, were answered in full by 612 of the 732 nurses still living, or 83.5 per cent. Roentgenographic examinations of the lungs were obtained and reviewed on 300 of the total group, or 40 per cent.

Detailed information, in addition to the questionnaires, was obtained concerning health and occupation through families, classmates, private physicians, Army, Navy, Veterans Administration, and the Public Health Service. This applied especially to those who were uncooperative, and sufficiently accurate information was obtained to make us believe that almost every case of tuberculosis was unearthed. Therefore the over-all figures are based upon the entire group of 745 nurses.

There were 71 cases of tuberculosis. Detailed information is lacking concerning one individual whose death from tuberculosis was officially reported. The roentgenograms of two cases were not obtainable for review but descriptions of the lesions were available as to location and size.

It is the purpose of this study to present the clinical data of a long term follow-up of tuberculosis. Discussion of the subjects of so-called "primary" and "reinfection" disease in young adults will center primarily around the clinical course, treatment, and prognosis of the 71 cases of tuberculosis which developed following admission to training until the close of the observation period. No nurse is included in the study with an observation period of less than five or more than fifteen years.

OBSERVATIONS

Incidence of Tuberculosis

It is of interest in the first place that the tuberculin negative and positive reactors were almost equally divided on admission (table 1).

Secondly, while somewhat more tuberculosis appeared in the initial non-reactors over the fifteen years, there was no statistically significant difference in the total amount of disease appearing in the two groups (table 2).

Fifty-two, or 14 per cent, of the non-reactors remained negative throughout training. Therefore, if the total amount of tuberculosis in the initially positive reactors is compared with the amount of disease which appeared in those who *converted* from "negative" to a "positive" tuberculin test, there is a noticeably higher incidence of tuberculosis in the group which "*converted*" (table 3).

The 71 cases of tuberculosis include one case of cervical lymphatic disease proved by biopsy, 66 cases of pulmonary tuberculosis, and 4 cases of pleurisy

TABLE 1

Number and Per Cent Distribution of All Nurses Studied, Classified by Result of Initial Tuberculin Test: 1932–1948

RESULT OF INITIAL TUBERCULIN TEST	ALL NURSES STUDIED	
	Number	Per cent distribution
All results	745	100.0
Reactors on entry	374	50.2
Non-reactors on entry	362	48.6
Result of initial test unknown	9	1.2

TABLE 2

Number and Per Cent of Nurses Studied Who Developed Tuberculosis, Classified by Result of Initial Tuberculin Test: 1932–1948

RESULT OF INITIAL TUBERCULIN TEST	ALL NURSES STUDIED		
	Total	Those who developed tuberculosis	
		Number	Per cent of total
All results	745	71	9.5
Reactors on entry	374	31	8.3
Non-reactors on entry	362	40	11.0
Result of initial test unknown	9	—	—

TABLE 3

Number and Percentage of Initial Non-reactors, among Nurses Studied Who Subsequently Developed Tuberculosis, Classified by Status of Reaction throughout the Training Period: 1932–1948

STATUS OF REACTION THROUGHOUT TRAINING PERIOD	ALL INITIAL NON-REACTORS		
	Total	Those who ddvelopd tuberculosis	
		Number	Per cent of total
All groups	362	40	11.0
Converted to positive	285	38	13.6
Remained negative throughout	52	2*	3.8
Status of reaction unknown	25	—	—

* Developed subsequent to training period after late conversion of tuberculin.

with effusion without demonstrable parenchymal disease. Hereinafter the mention of tuberculosis in "negative" or "initially negative" reactors implies that the "negative" tuberculin test had turned positive.

Thirdly, there was a closely parallel course in the rates at which tuberculosis appeared each year after entrance into training in the two groups of tuberculin reactors, expressed in rates per 1,000 observation years (figure 1).

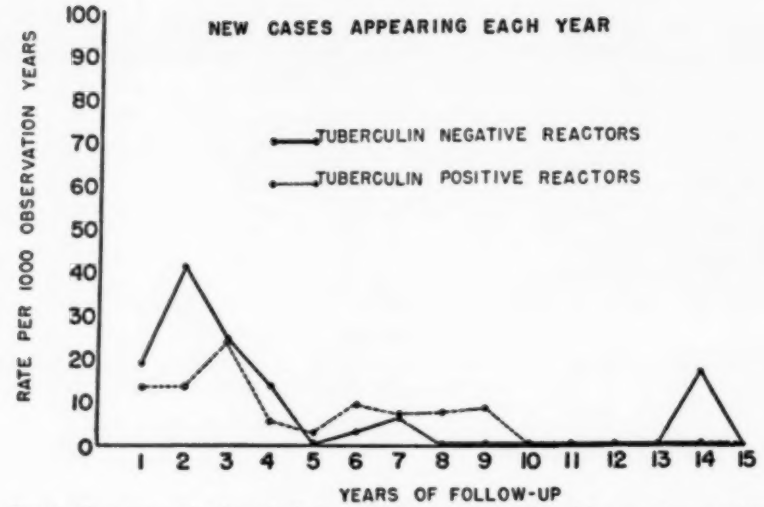

FIG. 1. Case rates of tuberculosis in initially negative and positive reactors per 1,000 observation years.

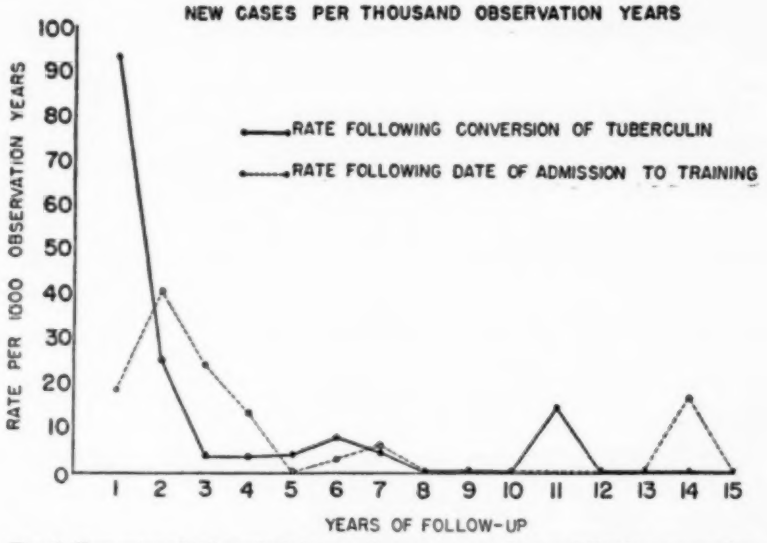

FIG. 2. Case rates of tuberculosis in negative reactors each year following conversion of tuberculin *compared to* their appearance following admission to training.

If the tuberculosis of the negative reactors on admission is analyzed, however, and its appearance in years from date of entry is compared with its appearance

in years following date of "conversion" from tuberculin negative to positive, a different picture is presented (figure 2).

In table 4 may be seen the number and per cent of new cases occurring each year and during each five year period. The appearance of new cases in both groups of reactors following admission to training, as well as appearance in time following conversion of tuberculin, are compared. In the initially negative reactors 55 per cent of the tuberculosis appeared within two years after admission to training while 32 per cent of tuberculosis in initially positive reactors appeared

TABLE 4

New Cases among Reactors and Non-reactors upon Admission and among Non-reactors after Conversion, Classified by Year: 1932–1948

YEAR	REACTORS UPON ADMISSION		NON-REACTORS UPON ADMISSION		NON-REACTORS AFTER CONVERSION	
	Number	Per cent distribution	Number	Per cent distribution	Number	Per cent distribution
1 to 15 years	31	100.0	40	100.0	40	100.0
1 to 5 years	22	70.9	36	90.0	36	90.0
1 year	5	16.1	7	17.5	26	65.0
2 years	5	16.1	15	37.5	7	17.5
3 years	9	29.0	9	22.5	1	2.5
4 years	2	6.5	5	12.5	1	2.5
5 years	1	3.2	—	—	1	2.5
6 to 10 years	9	29.0	3	7.5	3	7.5
6 years	3	9.7	1	2.5	2	5.0
7 years	2	6.5	2	5.0	1	2.5
8 years	2	6.5	—	—	—	—
9 years	2	6.5	—	—	—	—
10 years	—	—	—	—	—	—
11 to 15 years	—	—	1	2.5	1	2.5
11 years	—	—	—	—	1	2.5
12 years	—	—	—	—	—	—
13 years	—	—	—	—	—	—
14 years	—	—	1	2.5	—	—
15 years	—	—	—	—	—	—

in the same period. These values are to be compared with the 85 per cent of disease demonstrable in the initially negative two years following the date of *conversion of tuberculin to positive.*

At the end of the first five year period there is a close approximation in the rate of appearance of tuberculosis in all three groups.

Deaths from Tuberculosis

The 4 who died of tuberculosis were divided between "negative" and "positive" reactors. In the "negatives" both were far advanced disease when discovered. One (Case 1, appendix) developed her disease three years after completion of training, while she was a patient in a psychiatric institution. She died

four months after the initial diagnosis, with rapidly progressive bilateral tuberculosis. The other (M. R. Case 33, appendix) is described below. She died eighteen months after the acute pneumonic onset of her disease.

In the 2 "positives" who died, one (Case 46, appendix), is known to have died after finishing training, according to the records of the Massachusetts Department of Public Health and information from her classmates. Details of onset and course were not obtained.

The other (Case 50, appendix), developed minimal disease at the end of the first year of training. She received sanatorium care, left against advice, broke down again, was readmitted two years later, again left against advice and died of massive hemorrhage at home.

The 3 very interesting cases of disseminated lupus erythematosus have been reported elsewhere (11).

TABLE 5

Deaths among Nurses Studied, Classified by Cause of Death: 1932–1948

CAUSE OF DEATH	TOTAL DEATHS
All deaths	13
Tuberculosis	4
Lupus erythematosus disseminata	3
Accident and suicide	2
War casualties	2
Staphyloccus septicemia	1
Carcinoma	1

The Character of Tuberculosis in the Tuberculin Negative and Positive Reactors

A brief outline of all 71 cases of tuberculosis is found in the appendix, and the following case histories in more detail are samplings of only a few of the similarities and differences that existed in the tuberculosis which developed in the two groups of tuberculin reactors.

Case Reports

Progressive minimal disease in an initially negative reactor:

Case 1, M. H. C. (Case 8, appendix): The patient was an 18 year old, very blond young nurse, who was admitted to training with a *negative* tuberculin test in September 1932. In July 1934, her tuberculin test was first postive, in association with a fever of undertermined origin which appeared along with subjective involvement of some of the smaller joints. She was hospitalized at that time (July 1934) where she remained at bed rest. A thorough search for the cause of low grade fever was made and it was finally decided that it was probably rheumatic in origin. The patient was discharged home in December 1934, after five months of bed rest, and she returned to duty in January 1935 feeling well. A week after starting work, she fainted on the ward, was hospitalized again, and was found to have fever (100° F.) with some recurrence of joint pain. She was transferred to a hospital for rheumatic fever. Here she was symptom-free for a few weeks, then showed a slowly rising temperature. Three months after admission she developed cough and sputum. A roentgenogram of the

chest showed extensive infiltration of the left upper lobe and many tubercle bacilli were present in the sputum.

On subsequent review of the roentgenogram, it was noted that in July 1944 a small area of infiltration, 1.0 cm. in diameter, was present in the periphery of the left third interspace. This density had not been seen during her hospital admission. Moreover, in January 1935, when she returned to work, there was a node in the region of the right hilum which was not visible on previous or subsequent films. The patient subsequently developed tuberculosis of the sacroiliac joint which necessitated confinement in a cast for eighteen months. In addition, a left artificial pneumothorax was maintained for six years. At present a small, residual, well-calcified lesion is present in the apex of the left upper lobe. The patient is living a normal life, with a full-time job.

This girl with a negative tuberculin test initially was found to be tuberculin-positive when she developed her first infection with tuberculosis. Her minimal lesion progressed to far advanced disease in spite of eight months of bed rest. Her joint symptoms, her active sacroiliac disease, and her pneumonic spread suggest a hematogenous spread of her tuberculosis.

Progressive minimal disease in an initially positive reactor:

Case 2, A. C. H. (Case 56, appendix): The patient was a 19 year old girl who was *tuberculin*-positive and had a normal chest roentgenogram on entrance to the training school. She developed a 1.5 by 2.0 cm. lesion in the right midchest two years after admission to training. She was entirely symptom-free and no abnormal findings could be elicited on physical examination. Another roentgenogram one month later showed what was thought to be a central highlight. On re-examination four days later, however, this abnormality was no longer visible and at no time subsequently did it reappear. She remained at part-time work with extra rest. Roentgenograms of the chest were repeated at monthly intervals and the size of the lesion steadily diminished and the patient felt well.

In spite of her good progress, nineteen months after the first lesion was seen, there appeared on routine examination a new 5.5 by 2.5 lesion at the left apex. Once again it was entirely asymptomatic and without physical signs. She was hospitalized and given bed rest along with left artificial pneumothorax for eleven months. The latter was then abandoned as unsatisfactory after two pneumonolyses. No further complications occurred. Her recovery was uneventful and at present she is well, with both lesions well calcified, and is able to work full time.

This case represents reactivation of tuberculosis in a *positive* reactor. The course of events is probably very similar to the preceding case except for the long hiatus of well-being during which she remained on duty, between the appearance of the first lesion and the second one on the opposite side.

A healing minimal lesion in an initially negative reactor while on duty:

Case 3, M. C. S. (Case 38, appendix): This 18 year old girl entered training in September 1935, with a *negative* tuberculin test and a negative roentgenogram of the chest. Because of a severe streptococcus pharyngitis two months after admission, she stopped training and was readmitted in the next class five months later. At this time her tuberculin test was *strongly positive* to 0.001 mg. of Old Tuberculin. Roentgenographic examination of her chest revealed a homogenous density 1 by 3 cm. in the periphery of the right first interspace. She refused treatment but was cooperative in her monthly check-up. No further sign of her lesion could be seen after five months, but in October 1947 an irregular calcified deposit was noted at the site of her early lesion. At present she is entirely well and able to manage her household, which includes one-year-old twins.

This patient represents what must have been a "first infection" with tuberculosis in one whose resistance was good. Her pattern was parenchymal disease without demonstrable regional lymphatic enlargement.

The healing of a minimal lesion in an initially tuberculin-positive Negro girl while on duty:

Case 4, E. W. P. (Case 66, appendix): This 19 year old Negro girl came to training in September 1942, with a *positive* tuberculin test and a negative chest roentgenogram. Eleven months after admission she developed, without symptoms, a ground-glass comet-like lesion 1 by 1.5 cm. in the right third anterior interspace immediately below the interlobar septum, apparently in the right middle lobe. Because of the war and the shortage of beds in both sanatorium and hospital, she remained at work under close monthly clinical and roentgenographic examinations. By October 1946 the lesion was smaller, retracted and fibrotic, and by 1948 it apparently consisted of small calcium deposits. The patient is well and working full time now.

There is no reason to suppose that this small asymptomatic lesion was other than a first infection similar to the preceding case, which became manifest by roentgenogram within the first year of entering training. This Negro girl also showed extraordinarily good constitutional resistance. Her disease consisted of a small parenchymal lesion without demonstrable regional lymphatic enlargement.

Acute exudative tuberculous lobar pneumonia in an initially negative reactor:

Case 5, M. R. (Case 33, appendix): This 18 year old girl, who entered training in September 1935, remained tuberculin-negative through May 1936. On September 5, 1936, she was admitted for minor urinary symptoms following a bad cold of a week's duration. She had had a "stuffy" nose and an unproductive cough, without fever.

Following admission to the hospital she rapidly developed high fever with pneumonic consolidation of the entire left upper lobe, over a ten day period. Her sputum became positive for acid-fast bacilli and her tuberculin test was positive for the first time. Transferred to a sanatorium, she was given artificial pneumothorax, did well for about a year, then developed another pneumonic spread to the right side with cavitation. She died 18 months after the onset of her disease.

This acute pneumonia lesion appearing three months after a known *negative* tuberculin test must once again represent a first infection with tuberculosis in an individual of high sensitivity to the tubercle bacillus and low bodily resistance.

Acute exudative lobular pneumonia in a tuberculin positive reactor:

Case 6, E. P. C. (Case 47, appendix): This 18 year old girl, admitted to training in 1938, was tuberculin-*positive* with a negative roentgenogram and a normal physical examination. Fifteen months after admission in December 1939, she developed a pneumonic lesion in the upper third of the right lower lobe and tubercle bacilli were present in the gastric washings. Under sanatorium bed rest, she developed a cavity. She was given pneumothorax in February 1940, but the disease spread in March 1941 to the left side. In September 1941, she left the sanatorium against advice, married, and did well at home for a year and a half, maintaining her right pneumothorax. She returned in May 1943 with active disease. A left pneumothorax was induced and the right lung was re-expanded. In February 1947, the left pneumothorax was abandoned because of an obliterative pleuritis. Sputum and gastric washings have been negative for *M. tuberculosis* by examination and culture since 1944. The patient's disease is arrested and she is living a normal life.

There would seem to be very little difference between this and the preceding case. Both were acute pneumonic lesions, varying only in the anatomical extent of lung involvement. The first, a pneumonic lesion in a girl tuberculin-negative three months before onset; the second a pneumonic lesion in one tuberculin-positive at entrance. Neither presents any clinical or roentgenographic distinctions which would classify it as a primary as opposed to a reinfection type of tuberculosis. From the clinical standpoint, the disease of both patients apparently represents the same thing, a first infection, or more simply, progressive pulmonary tuberculosis.

Pleurisy with effusion in an initially negative reactor:

Case 7, J. F. A. (Case 3, appendix): This 19 year old girl was admitted to training in February 1932. She had a negative chest roentgenogram and a *negative* tuberculin test which turned positive six months after admission. In February 1933, one year after admission, a routine chest roentgenogram revealed a small mottled infiltration one sq. cm. in size in the lower segment of the right upper lobe, associated with significant enlargement of the regional hilar lymph nodes. For two days she had had a very slight pleuritic pain in the right mid-axilla without fever, cough, or loss of weight. She was removed from training and sent home on twenty-two hours' bed rest a day, which she is said to have observed for four months. Five months after the appearance of her parencyhmal lesion on the right she had a bad "head cold." Two weeks later she developed an acute febrile serofibrinous pleurisy with effusion on the right, for which she received eight months of sanatorium care. Shortly after discharge she was married against advice and had three children, without exacerbation of her tuberculosis. Today she remains well and has brought up her whole family without further reactivation of her tuberculosis.

She was the first case of pleuristy with effusion definitely shown to follow in the wake of primary parenchymal infection after conversion of the tuberculin test from negative to positive.

Pleurisy with effusion in an initially positive reactor:

Case 8, H. K. (Case 59, appendix): This 18 year old nurse was admitted to training in February 1942, with a *positive* tuberculin test. In April, two months after entering training, she had a slight pleuritic-like pain in the left lower chest, with a negative roentgenogram of the chest. In May, three months after admission, she had a similar but less severe pain in the right lower chest. In June, four months after admission, she developed a small infiltration in the left infraclavicular area followed in July by a small serous effusion of the right chest. For this she took three months of sanatorium care, until October 30th. She returned directly to duty, obviously too soon, as she developed acute pleurisy with effusion on the left, together with visible enlargement of a left hilar lymph node. She received seven more months of sanatorium care. An accidental pneumothorax accompanied a chest tap on the left. Following sanatorium treatment, her disease remained arrested until 1947, when a tuberculous salpingitis was surgically removed in June of that year. At present this patient's lesions are arrested. She is married and has no children.

Classification and Treatment

The lesions which we have encountered have for the most part been small pulmonary infiltrations 1 by 2 cm. in diameter with none larger than 6 by 8 cm. in the minimal group. They are classified in table 6.

Bed rest, in both "sanatorium" care and "home" treatment, included bathroom

privileges except for the few who were cared for at the Boston City Hospital where *absolute* bed rest was imposed. For the minimal lesion, six weeks to fourteen months of bed rest was instituted for those who needed no collapse therapy. The average period of bed rest was five and one-half months in both the initially negative and positive tuberculin reactors for minimal lesions.

TABLE 6

Cases of Tuberculosis Which Developed among Initial Tuberculin Reactors and Non-reactors Studied and Classified by Initial State of Disease: 1938–1948

STAGE OF DISEASE	CASES OF TUBERCULOSIS AMONG		TOTAL CASES OF TUBERCULOSIS AMONG NURSES STUDIED	
	Initial reactors	Initial non-reactors	Number	Per cent distribution
All stages	31	40	71	100.0
Pulmonary	30	36	66	92.9
Minimal	22	32	54	76.1
Moderately advanced	7	2	9	12.7
Far advanced	—	2	2	2.8
Stage of disease unknown	1	0	1	1.4
Pleurisy with effusion	0	4	4	5.6
Tuberculous adenitis	1	—	1	1.4

TABLE 7

Specific Treatment in 71 Nurses

	INITIAL REACTORS, NUMBER	INITIAL NON-REACTORS, NUMBER	TOTAL	
			Number	Per cent
Bed rest only	11	22	33	46.5
Bed rest plus pneumothorax	9	7	16	22.6
Bed rest plus thoracoplasty	2	0	2	2.8
O.P.D. supervision only	6	9	15	21.1
O.P.D. plus rest	1	0	1	1.4
O.P.D. plus pneumothorax	1	1	2	2.8
Unknown course	1	1	2	2.8
Total	31	40	71	100.0

Four to eight months of slowly increasing exercise characterized the convalescence in the uncomplicated cases. The classification of "Out-Patient Department supervision" was a routine of regular monthly general physical, roentgenographic, and laboratory examination. This group of nurses remained on duty and, with the cooperation of the training school, was usually permitted a midday rest, supplements to diet, and relief from night duty as long as was requested. These girls were indeed "treated" and were watched with the utmost care.

In table 7 may be seen the specific treatment procedures used in the two groups of initially negative and positive reactors.

Table 7 is self-explanatory with the exception of the cases supervised in the Out-Patient Department (O.P.D.). A total of 18 were carried on this regimen. Fifteen received no definitive treatment while they remained at work, except regular O.P.D. supervision. In 3 patients the lesions reactivated. One of these showed extension of her minimal lesion two years after its discovery and was treated with pneumothorax. A second (Case 2), 19 months after satisfactory regression of her small initial lesion, developed an asymptomatic spread to the contralateral apex. The third, classified as "O.P.D. supervision," had an unreported pleurisy and twelve months later developed an apical infiltration treated with bed rest. Another patient (Case 24, appendix) is recorded as having had a "reactivation" but in reality she had a very small asymptomatic pleural effusion associated with a very small parenchymal infiltration. She was allowed to remain on duty with careful check-up and her disease has shown no reactivation in the ten succeeding years. In view of our present regard for tuberculous effusions, this girl would not be allowed to remain on duty with this lesion today.

It should be made clear at this point that all early tuberculous lesions were considered potentially progressive. When symptoms of activity also accompanied the visible roentgenographic infiltration, however, small, there was no question of the need of bed rest treatment. A careful, scrupulously detailed history remains a great necessity in these cases. Too much emphasis is likely to be placed upon the roentgenographic appearances alone. The physical examination of the lungs with these small lesions was almost always negative, but the *general physical* examination often revealed defects which were thought to bear an untoward effect on the progress of the infection.

Pleurisy with Effusion

A total of 12 individuals had pleurisy with effusion, but one patient had two episodes. Nine cases appeared in the initially negative reactors, 3 cases in the "positive" reactors. Four of those in the initially negative reactor group followed several months after the appearance of a parenchymal lesion (Cases 3, 15, 59, appendix). Four cases were associated with demonstrable pulmonary disease (Cases 24, 25, 48, 67, appendix). Four cases showed no roentgenographic evidence of parenchymal disease (Cases 12, 23, 28, 36, appendix). The thirteenth episode (Case 59, appendix), was the appearance of a pleural effusion on the side contralateral to the original effusion four months previously. In the 4 patients whose pleurisy with effusion followed the appearance of a parenchymal lesion, the interval of time between the two episodes was seven months in Case 3, thirty-four months in Case 15, four months in Case 40, and two months in Case 59.

This sequence of events of pleural effusion following a minimal parenchymal lesion with and without visible lymphatic enlargement was seen in initial reactors and non-reactors. It gives visible proof of at least one pattern which is seen in the pathogenesis of pleurisy with effusion. Spread from a parenchymal lesion to the sensitized pleura may be direct by extension from a subpleural lesion or, as seems very likely but less easily proved, by the lymphatics and the blood stream to the sensitized pleura. The course of events in Case 3, with the greatly en-

larged regional lymph nodes, suggests the hematogenous route as does Case 15 with the effusion contralateral to the parenchymal disease, and Case 59 with its bilateral effusion following the left-sided parenchymal disease. It appears in these cases that pleurisy with effusion has developed as an expression of a more generalized phase of tuberculous infection after primary localization. Strictly speaking, it is an exacerbation or reactivation of primary parenchymal infection. A true primary complex of Ranke (10), with lymphatic involvement and spread to the pleura by the blood, may occur. Since the lung is the most common site of primary infection in this country, most cases of pleurisy with effusion must follow pulmonary infection. It is logical to assume, however, that bacilli from primary intestinal disease with its extensive lymphatic involvement may be another source of bacilli blood borne to an allergic pleura.

TABLE 8

End Results of Minimal Tuberculosis

MINIMAL TUBERCULOSIS (54)	INITIALLY NEGATIVE (32)		INITIALLY POSITIVE (22)		TOTAL (54)	
	Number	Per cent	Number	Per cent	Number	Per cent
A. *End Results*						
Finally arrested	29	90.7	19	86.4	48	88.8
Under treatment	2	6.2	2	9.1	4	7.4
Dead	0	0.0	1	4.5	1	1.9
Unknown	1	3.1	0	0.0	1	1.9
Total	32	100.0	22	100.0	54	100.0
B. *Reactivations*						
Infiltrates	6		7		13	
Pleural Effusions	4		3		7	
Total	10		10		20	

Thus each of the eight cases of pleurisy with effusion in this series which followed parenchymal disease, or was associated with it, is classified according to the nature of pulmonary infiltration. The pleural effusion itself is classed as a *reactivation* in each of these 8 individuals. Only the 4 cases of pleurisy with effusion *without* any visible parenchymal lesion are classed initially as pleurisy with effusion. Even though it be assumed that the primary lesion in these 4 cases was in the lung and was not detected by the roentgenographic examinations at six month intervals, or was too small to be seen, the primary infection may have been intestinal in origin.

End Results of Tuberculosis

The end results of the 71 cases of tuberculosis are shown in tables 8, 9, and 10. Arrested tuberculosis also includes cases which are apparently healed. Unexpanded pneumothorax is classed as still "under treatment." *Reactivations* in-

clude asymptomatic roentgenographically demonstrable spreads of disease as well as clinically significant "spreads." Only pleurisy with effusion without visible lung disease is classed initially as such. "Reactivations" apply only to those whose lesions have been "arrested" and who developed a new lesion or pleurisy with effusion at some subsequent date.

Table 8, Section A, presents the end results of initially minimal tuberculosis. Eighty-nine per cent of the patients are living a normal life and their disease is arrested. Of the 5 still under treatment, one is receiving pneumothorax but clinically is apparently arrested. The one patient who died left the sanatorium

TABLE 9

End Results of Moderate and Far Advanced and Extrapulmonary Tuberculosis and Pleurisy with Effusion

	INITIALLY NEGATIVE	INITIALLY POSITIVE	TOTAL
A. *Moderately and far advanced (11)*			
Finally arrested	0	6	6
Under treatment	2	1	3
Dead	2	0	2
Extrapulmonary (1) (Adenitis)	0	1	1
Initial classification unknown	(1)0	1 (dead)	1
B. *Pleurisy with effusion* (4) (no infiltration of lung)			
Finally arrested	4	0	4
Reactivations	2	0	2
Dead	0	0	0
	4	0	4
C. *Summary*			
Totals of Table 9	8	9	17
Totals of minimal disease (Table 8)	32	22	54
Grand total	40	31	71

against advice and her disease progressed rapidly to fatal hemorrhage. Reactivations, Section B, occurred as parenchymal disease in 13 patients. In one individual the reactivation was an incidental finding on roentgenographic examination, was arrested at the time, and was not associated with a history of symptoms. Of 13 patients with parenchymal reactivations, 3 are still under treatment, one died of hemorrhage, and 9, or 68 per cent, have arrested lesions at present.

Seven cases of pleurisy with effusion in this group are classed as reactivations because they followed or were associated with pulmonary lesions. One was a pleurisy on the side opposite the pulmonary infiltration and one was a bilateral effusion followed five years later by tuberculous salpingitis which was successfully treated surgically.

Table 9, Section A, presents the end results of moderately and far advanced disease and extrapulmonary disease. Section B presents pleurisy with effusion without lung infiltratres. The number of cases is presented rather than percentages as the totals are small. Section C summarizes the totals in numerical figures only.

Table 10 summarizes the total reactivations of the series. Two reactivations would not have been known except for a review of roentgenograms made in retrospect. The lesions in both of the patients are now arrested. Of the 16 patients with reactivations, 4 are under treatment, one is dead, and 11 have arrested lesions and are married or working and living a normal life.

Thus these three tables, 8, 9, and 10, again show the similarity of distribution of disease and end results as seen in the initially negative and positive reactors.

TABLE 10

*Total Reactivation in 71 Cases of Tuberculosis**

	INITIALLY NEGATIVE	INITIALLY POSITIVE	TOTAL	PER CENT
Parenchymal Infiltrate	7	9	16	22.5
Symptomatic			14	19.7
Asymptomatic			2	2.8
Pleural Effusion	4	4	8	11.2
Total	11	13	24	33.7

* Initial Case Distribution
66 Cases of pulmonary tuberculosis
4 Cases of pleurisy with effusion
1 Case of tuberculous adenitis.

Tuberculosis Case Rates[4]

This relatively small group of nurses had a total of 71 cases of tuberculosis, but the group was followed for five to fifteen years. Thus the over-all 71 cases of tuberculosis with 7,492 observation years from 1932 to 1948 give an attack rate of .95 per hundred per year. Fifty-six of these 71 lesions required treatment and present a rate of .74 per 100 nurses per year.

The 15 very small lesions were those O.P.D. supervised cases which might well have never been recognized but for regular six month roentgenographic examinations which revealed their presence and their uneventful regression. There is little doubt that the roentgenographic visualization of the lesion alone is deceptive as it may have little or no clinical significance. Very careful and frequent observation is necessary to establish the character of these small lesions.

Forty-five new treated lesions occurred *during training* in the 745 nurses with a case rate of 2.0 per hundred per year. Eleven treated cases occurred in the nurses *after graduation*, with a rate of 0.20 cases per hundred per year. Each group is based on its respective total observation years.

[4] Statistical data and rates were reviewed by Miss Jane Worcester, Assistant Professor of Bio-statistics, Harvard School of Public Health.

These figures are computed on the basis of those 745 nurses who comprise the follow-up study.

A total of 1,203 nurses, however, was admitted to the Training School, of whom 458 resigned for failure in studies or nontuberculous illness. These totaled 493 additional observation years. Fifty-six nurses who developed new tuberculous lesions requiring treatment were dropped statistically from observation at the time their disease developed. These totaled 356 observation years. Thus the corrected total observation years for all nurses admitted to training, minus those removed from training or observation for all causes, is 7,629. The overall rate for all 71 lesions is .93 per 100 nurses per year. For the 56 nurses needing specific treatment the rate is .73 per hundred per year.

DISCUSSION

The incidence of tuberculosis in initially "negative" and "positive" reactors to tuberculin: This horizontal study of tuberculosis in nurses reemphasizes certain concepts concerning the pathogenesis of the disease which formed the basis of an earlier report on this same group of nurses by one of the writers (T. L. B.) (2). At that time there appeared to be few or no clinical and roentgenographic features to distinguish the tuberculosis which developed, whether it occurred in reactors or non-reactors to tuberculin on admission to training. Clinically the same type of tuberculosis was observed in both groups of individuals. The factor that *seemed* most important in determining the pattern of disease and the course in infection was the individual's inherent constitutional resistance to tuberculosis or her lack of it. This longer fifteen year follow-up report substantiates those earlier observations and helps to clarify our own wavering conceptions of the pathogenesis of this disease.

The close parallelism of incidence of tuberculosis in "negative" and "positive" reactors in our nurses does not seem remarkable, although at variance with some other reports. It is to be expected that different results will be obtained in different hospitals, and among different age groups, and in other countries. Racial as well as individual and environment factors will influence the findings.

Shipman and Davis (5) found that most of their nurses who developed clinical tuberculosis during training were tuberculin-positive on entrance. Pollack and Cohen (12) also found a closely similar rate of tuberculosis in both negative and positive reactors, as did Israel and Long (13). On the other hand, Geer (6), Heimbeck (14, 15), Amberson and Riggins (16), and Rist (17) show far more tuberculosis in the initially negative reactors.

These results are outlined as extracted from the Prophit Survey (18) in England. The sequence has been rearranged by the present writers.

One of the present writers (T. L. B.) in an earlier report (2) found 8 cases of tuberculosis in the negative reactors compared to one in the "positives" in a short term study of a few cases. But the accumulation of cases of tuberculosis and the passage of time in follow-up has shown a constant leveling off of differences in the two groups over the years. The three year training period has become an artificial unit of time for observation in such studies as this. The tu-

berculin test remains the diagnostic standard for the presence or absence of tuberculous infection.

The reason for the high morbidity in the "positive" group on entry is not clear. It seems most logical to account for it on the basis of the natural history of tuberculosis in young women, for the morbidity is normally highest in this age group. The peak of disease in this "positive" group lags behind that of the "negatives," nor is it at any time as high a rate. Removal of the more susceptible nurses with active cases of tuberculosis before they could apply for nursing school may account for this difference in the two curves of morbidity, but it seems an unimportant influence. Both groups had theoretically the same exposure to tubercle bacilli during their training, with working hours and living

TABLE 11*

OBSERVER	YEAR	GROUP	FIRST EXAMINATION TUBERCULIN-POSITIVE			FIRST EXAMINATION TUBERCULIN-NEGATIVE		
			Total	Cases TB	Per cent	Total	Cases TB	Per cent
Shipman & Davis (5)	1933	Nurses	96	7	7.3	47	2	4.3
Pollack & Cohen (12)	1941	Nurses	419	7	1.7	280	5	1.8
Israel et al (14)	1941	Nurses	360	34	9.4	277	34	12.3
Geer (6)	1934	Nurses	87	1	1.1	204	8	3.9
Heimbeck (15, 16)	1936	Nurses	625	20	3.2	412	57	13.8
Amberson & Riggins (17)	1936	Nurses	285	2	0.7	207	6	2.9
Rist (18)	1939	Nurses	84	0	0.0	60	6	10.0
Comparing this study ▮ Badger & Ayvazian	1948	Nurses	374	31	8.2	362	40	11.0

* From the Prophit Survey (18).

conditions the same. Diet was fundamentally the same, subject to variations imposed by the idiosyncrasies of young women concerning their weight.

Primary vs. reinfection tuberculosis: The pathogenesis of tuberculosis has for many years been thought of in terms of primary or "childhood type" tuberculosis and reinfection or "adult type," each tending to be differentiated into its own rather characteristic clinical and prognostic pattern. Tuberculin and roentgenographic surveys of children and young adults during the past twenty years have conditioned our thinking in terms of tuberculin-negative and -positive reactors, again each with its own type of lesion. "Primary" or "childhood type" tuberculosis was pictured as occurring in non-reactors who turn positive, and "reinfection" or "adult type" tuberculosis as occurring in those who were already positive to tuberculin. Moreover, there has been a prevailing view that "primary" tuberculosis is a relatively benign disease compared to that of "reinfection" type.

Ghon (9) and Ranke (10) first wrote of "primary" tuberculosis as a "childhood" disease and "reinfection" tuberculosis as its "adult" form. Epidemio-

logic changes in the morbidity and mortality of tuberculosis have altered our attitude towards these earlier concepts, chiefly because large sections of the population now do not develop their first or "primary" infection until the second, third, or fourth decades of life.

The Prophit Tuberculosis Survey (18), published in 1948, in its very interesting study of tuberculosis in the British Isles speaks of primary and reinfection disease as follows (paragraph 2, page 184):

> It is recognized by all, except a few who believe that pulmonary tuberculosis in young adults is usually the result of a primary infection, that reinfection is responsible for much, or indeed most adult tuberculosis. The two terms, "adult" and "reinfection" tuberculosis, are used synonymously.

Such conclusions are not in accord with our clinical observations, nor with recent pathological studies which will be described.

Terplan (19), in his exhaustive pathological studies of human tuberculosis, presents the evidence for primary infections up to the age of 80 years. He shows that the pattern of healed primaries is the same for all age groups and exists in the lung parenchyma with and without regional lymphatic involvement. He feels that the development of tuberculin sensitivity should not be made the dividing line between "primary" and "reinfection" tuberculosis. Sensitivity to tuberculin occurs soon after the initial lodgement of tubercle bacilli in the body, but there is no sound basis for regarding a positive tuberculin test with the development of allergy as the criterion of "reinfection".

Lurie (20) in 1944 presented the results of years of experimental study with tuberculosis in numerous strains of inbred rabbits with *known* variations in their inherited constitutional resistance to tuberculosis. He found that there was *no* constant pattern of "primary" or "reinfection" tuberculosis. Those strains of rabbits with high resistance to tuberculosis could localize the naturally acquired primary infection in the lung parenchyma without any regional lymphatic involvement. But with similar exposure those with low natural resistance produced the familiar "primary complex" with regional lymph node involvement and infection in distant organs. A *single* artificial infection produced similar effects and different patterns of disease which varied according to the inherent resistance of the rabbit strain when the infecting doses were similar.

Medlar (21), in his pathological studies of *Primary and Reinfection Tuberculosis as a Cause of Death in Adults*, finds no clear-cut difference in the pathology of "primary" and "reinfection" tuberculosis in humans. He found the "primary" or first infection the usual cause of death from tuberculosis under the age of forty, but occasionally its cause up to sixty years. Beyond the age of forty, "reinfection" tuberculosis was more common. The term "reinfection" tuberculosis he uses only in the sense of a new infection from outside the body; new disease acquired in the presence of a former but obsolete and healed "primary." Thus, as Amberson points out, the differentiation of primary and reinfection tuberculosis is a pathological problem and not possible to distinguish clinically. But Medlar goes further in his pathological studies in feeling that

allergy does not play a very important part in determining the progress of the disease. He found primary and reinfection (in the strict sense) tuberculosis to be indistinguishable, on a pathological basis.

Constitutional factors: It is not clear what makes "primary" or "first infection" tuberculosis in one individual go on to subclinical healing throughout its course, while in another the process becomes progressive cavernous disease, and in still another it progresses from early pneumonic consolidation to a rapid death. The clinical observations of this study point to the importance of inherent constitutional resistance as being one of the most important influences in establishing the course and prognosis of each case. All our nurses had the same theoretical exposure to sputum "positive" cases of tuberculosis during training and experienced similar living and working conditions. *It is of importance that the initially tuberculin-negative and -positive groups developed not only a closely similar amount of tuberculosis but developed disease which was clinically comparable in both groups as seen by similar roentgenograms, similar treatment, and similar end results.*

It is of interest also that among the negative reactors on admission 14 per cent went through training without ever becoming tuberculin-positive. Perhaps these individuals were endowed with a very superior resistance to tuberculosis which destroyed the tubercle bacillus before it could establish a "beach head" in the body. Perhaps they were just lucky. Eighty-six per cent of those who did turn positive showed no roentgenographic or clinical evidence of tuberculosis and exhibited the presence of acquired infection only by a positive tuberculin test. Fourteen per cent of those who did turn positive showed roentgnographic evidence of tuberculous lesions. In approximately one-quarter of this group the lesions remained subclinical throughout the period of roentgenographically demonstrable disease. These groups must all have been endowed with good resistance to their tuberculosis.

Clinically, it has seemed to us and has been noted previously (2) that the inherent constitutional resistance of the individual to tuberculosis was the most important factor in determining the pattern of her disease. Lurie (20) makes it clear from his experimental studies that "the resistance of rabbits to naturally or artificially acquired tuberculosis is a function of their genetic constitution."

Medlar (21) states that the cause for progression in some primary infections is due to inherent qualities of susceptibility of certain parts of the lung, the apices of the lobes, when infection lodges in those areas. Thus the additive effects of frequent re-exposure may lead to development of disease by the greater chance of apical involvement.

However the case may be, good mechanical technique for breaking contact and spread of tubercle bacilli should be established, but dependence upon these technical factors of prevention should not be exploited at the expense of other measures. No matter what mechanical or immunological procedures are used in prevention, constitutional resistance, general health, fatigability, diet and nutrition, the way of living and psychological reactions to family, work, and recreation, all play their part and contribute to the response of the host to infection.

Comparison of our results with those of other similar studies carried on for fifteen years or more shows expected differences. Heimbeck in 1947 (23) reported a twenty year follow-up of his nurses at Ulleval Hospital, summarized under "Foreign Letters" in the Journal of the Americal Medical Association (23). His reported results are as follows:

	NUMBER NURSES	NUMBER CASES OF TUBERCULOSIS	DEATHS
Pirquet Positive	668	35	1
Pirquet Negative (BCG Vaccination)	501	42	5
Pirquet Negative (No BCG)	284	105	12

The above figures represent the accumulated results of his group of nurses during their three year training period only. His "second period" of observation includes the accumulated data of the seventeen years following completion of training. In this second group it is reported that there was essentially no difference in the morbidity or mortality in the above three groups of nurses.

The high incidence and high mortality rate in his "negative" unvaccinated nurses seems to indicate some racial differences in a greater susceptibility to tuberculosis in Norwegian nurses. The "positives" on entry to training suggest a true "survival of the fit" with earlier elimination of the susceptibles by the Darwinian process of "natural selection." Their exposure to tuberculosis must have come before they reached the age for training as nurses. Again in the unvaccinated "negatives" on entry, with their high morbidity and mortality, those susceptible to tuberculosis were eliminated under observation. Those who survived did as well in subsequent years as the "positives" on entrance to training. This would be expected.

This study of Heimbeck's has shown the usefulness of BCG vaccination in his nurses where results point to a racially greater susceptibility to tuberculosis and where the high morbidity and mortality suggest more severe disease and a greater risk of exposure to bacilli. The differences in results of these two long follow-up studies may well be explained on this analysis of racial and individual variations in constitutional factors.

Morbidity: The morbidity or case rates of this study compare favorably with that of other reported series. Childress (24) in his fifteen year study found an annual attack rate of 1.39 per 100 in student nurses. Amberson and Riggins (4) in a shorter study present a rate of 1.09 per 100 per year for over-all lesions, but 0.68 per hundred nurses per year for new pulmonary and pleural lesions requiring treatment. Our rate for new pulmonary and pleural lesions requiring treatment in the longer fifteen year follow-up was 0.73 per 100 per year, approximately the same as that of Bellevue, another large municipal hospital. This rate of 0.73 per 100 nurses per year for us is higher than that recorded in Childress' article (24), for clerks in the Metropolitan Life Insurance Company in New York of 2 to 3 per 1,000 per year, or 0.2 to 0.3 per 100 per year. The latter value, however, is similar to our annual rate of 0.2 per hundred after graduation.

It is believed that the length of our follow-up and the absence of other life tables outside the nursing profession of similar length does not permit a satisfactory comparative study. Our rates do, however, present a definite trend over the years and the long term picture is favorable. The attack rate at the time of highest known exposure, during training, is proportionately higher than during the post-training period. But the early discovery of the minimal lesion by routine six-month roentgenographic examinations shows 89 per cent of the nurses with arrested lesions, and working or living a normal life.

In a hospital community where control against contact with the tubercle bacillus has not been elaborate but basic, it appears that many factors already outlined contribute to the development of clinical tuberculosis, in addition to contact with the microorganisms. It is not enough to consider the individual lesion alone during the time a nurse is in training. In this study the detailed analysis of the progress of the disease is considered in the light of further understanding the pathogenesis of tuberculosis from clinical experience. The perspective granted by the fifteen year follow-up emphasizes the excellence of late results and the importance of the inherent constitutional capacity of young women to handle tuberculous infections successfully, when diagnosed and treated in the earliest stages.

SUMMARY

1. Seven hundred and forty-five nurses followed five to fifteen years have shown statistically the same amount of tuberculosis appearing in the initially negative and positive tuberculin reactors.

2. The findings offer little justification for any clinical differentiation into "primary" or "childhood" and "reinfection" or "adult" tuberculosis. The type of disease has been essentially the same in character, course, and prognosis in both groups.

3. The individual, inherent, constitutional resistance to tuberculosis has clinically seemed the most important single factor in determining the pattern of disease in this group of nurses over the years. Their similar age, sex, living and working conditions, their similar diet and exposure to tuberculosis have been fairly constant. Individual differences in the course of similar types of lesions have borne very little relationship to the duration or degree of allergy.

4. A discussion of primary or reinfection tuberculosis has led us to the conclusion that most, if not all, of the disease in this group has been primary, first infection tuberculosis, whether it appeared in the initial reactor or non-reactor to tuberculin.

5. These studies have shown that the first infection, or "primary" tuberculosis, as seen in the initially negative tuberculin reactors, may go on to progressive destructive tuberculosis of almost any type. It may, in the other extreme, become rapidly arrested with clearing of the shadow on the roentgenogram and at no time give constitutional or local signs or symptoms of clinical tuberculosis. All gradations of the disease may appear between these extremes. The tuberculosis which appeared in the initially positive reactors acted in the same man-

ner. Thus the state of allergy appears to play less part in the pathogenesis of the disease than do inherent constitutional differences in resistance to tuberculosis, together with environmental factors and treatment.

6. The morbidity of this group compares favorably with that observed in other similar series. The final rate for all lesions is .93 per 100 nurses per year, while the rate for new pulmonary and pleural lesions needing treatment is .73 per 100 nurses per year.

SUMMARIO

La Tuberculosis en las Enfermeras: Observaciones Clínicas sobre su Patogenia según Revelan Quince Años de Vigilancia de 745 Enfermeras

1. Setecientas cuarenta y cinco enfermeras observadas de cinco a quince años han revelado sustancialmente la misma proporción de tuberculosis en las negativas y las positivas inicialmente a la tuberculina.

2. Los hallazgos ofrecen poca justificación para la diferenciación clínica en tuberculosis "primaria" o "infantil" y de "reinfección" o "adulta." La forma de la enfermedad fué esencialmente idéntica en naturaleza, evolución y pronóstico en ambos grupos.

3. La resistencia constitucional, inherente, individual a la tuberculosis pareció ser el más importante factor aislado en lo tocante a determinar el patrón de la enfermedad en este grupo de enfermeras a través de los años. La semejanza en edad, sexo, condiciones de vida y de trabajo, alimentación y exposición al mal fué bastante constante en ellas. Las diferencias individuales en la evolución de lesiones de forma semejante guardaron poquísima relación con la duración o la intensidad de la alergia.

4. Un estudio de si la tuberculosis era primaria o de reinfección lleva a la conclusión de que la mayor parte de la enfermedad, sino toda, en este grupo ha sido primoinfección, ya apareciera en las inicialmente negativas o positivas a la tuberculina.

5. Estos estudios demuestran que la primoinfección, o tuberculosis "primaria, tal como se observara en las inicialmente negativas a la tuberculina, puede avanzar a tuberculosis destructora progresiva de casi cualquier forma. Por otro lado, puede también estacionarse rápidamente con despejo de la sombra radiográfica sin manifestar en ninguna ocasión signos o síntomas orgánicos o locales de tuberculosis clínica. Entre esos extremos pueden presentarse todos los grados de la enfermedad. La tuberculosis que apareció en los reactores inicialmente negativos actuó en la misma forma. El estado de alergia parece, pues, desempeñar en la patogenia de la dolencia un papel menor que las inherentes diferencias orgánicas en la resistencia a la tuberculosis, unidas a los factores del ambiente y al tratamiento.

6. La morbidad en este grupo compárase favorablemente con la observada en otras series semejantes. El coeficiente final para todas las lesiones fué de 0.93 por 100 enfermeras por año, en tanto que para las nuevas lesiones pulmonares y pleurales que necesitan tratamiento es de 0.73 por 100 enfermeras por año.

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Reports and roentgenograms from Middlesex County, Plymouth County, Rutland State Sanatoriums, the Boston Sanatorium, and the Channing Home for Tuberculosis, as well as numerous Veterans Administration hospitals, contributed greatly to the completeness of the study. To all these we are greatly indebted for their assistance.

We are grateful to all the nurses whose loyalty to the study and whose repeated responses over the fifteen years have enabled us to fit the pieces of this picture puzzle together.

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APPENDIX

Table of Case Histories

Summaries

CASE NUMBER	DIAGNOSIS	LESION SIZE IN CM.	SYMPTOMS		PHYSICAL SIGNS	BACILLI	TREATMENT	PROGRESSION REACTIVATION	END RESULT
			Constitutional	Local					
Initially negative reactors									
1 R. I. A.	F. A.	Bilateral cavity	+	+	+	S. +	Pneumothora bilateral	Progression	Died
2 D. A.	Min.	1.5 by 2	0	+	0	G. +	Rest, home	0	A.. W.
3 J. F. A.	Min. lymphatic	1 by 2	0	0	0	0	Rest, 12 months	Reactivation Pleural effusion	A. M. 3 Ch.
4 L. B.	Min.	3 by 2	+	0	0	+	Rest (O. R. A. A.) 3 times	Reactivation 3 times	—M. 1 Ch.
5 R. L. B.	Min.	1 by 1.5	+	0	0	0	Rest, 6 weeks	0	A. W.
6 G. MeD. B.	Min.	1 by 2	0	0	0	0	O. P. D. only	0	A. M. 1 Ch.
7 G. F. C.	Min.	2 by 3	+	+	0	0	O. P. D. only	0	A. M. 3 Ch.
8 M. H. C.	Min.	1 by 1	+	0	0	+	Rest, 5 months Pneumothorax Re-expansion 1941	Progression 1 year	A. W.
9 A. R. C.	Min.	3 by 3	0	0	0	0	O. P. D. only	0	A. M. 2 Ch.
10 J. C.	Min.	1 by 2	+	0	0	0	Rest, 6 months	0	Under treatment
11 M. H. D.	Min.	2 by 2	+	0	0	0	Rest, 6 months	0	A. M. 1 Ch.
12 E. D.	Pleurisy with Effusion		+	+	+	0	Rest, 6 months	0	A. M. Accidental death
13 M. R. D.	M. A.	Bilat.	−	−	−	0	Rest, years	Reactivation kidneys, spine	Under treatment A. M. 1 Ch.
14 D. D.	Min.	1 by 1.5	0	0	0	0	O. P. D. only	0	A. W.
15 V. C. F.	Min.	1.5 by 2	0	0	0	0	Rest, 10 weeks	Reactivation Pleural effusion	A. M.
16 E. M. F.	Min.	3 by 4	+	+	+	?	Pneumothorax Re-expansion	0	A. W. M. 3 Ch
17 C. G.	Min.	3 by 4				0	?	0	A. W.
18 V. G.	Min.	3 by 4	0	+	0	0	Rest, 9 months	0	A. W.
19 H. U. K.	Min.	3 by 3.5	0	0	0	0	O. P. D. only	0	A. M.
20 B. M.	Min.	1 by 1	0	0	0	0	Rest, home	Reactivation 5 months rest	A. W.
21 M. M.	Min.	1 by 1	0	0	0	−	Rest, 6 months	Reactivation 6 months rest	A.
22 G. B. M.	Min.	2.5 by 3	+	0	+	G. +	Pneumothorax Re-expansion 1945	Reactivation	A. M. 3 Ch.

Table of Case Histories—Continued

CASE NUMBER	DIAGNOSIS	LESION SIZE IN CM.	SYMPTOMS		PHYSICAL SIGNS	BACILLI	TREATMENT	PROGRESSION REACTIVATION	END RESULT
			Constitutional	Local					
Initially negative reactors—Continued									
23 H. F. M.	Pleurisy with effusion		+	+	+	0	Rest, 2 months	0	A. M. 1 Ch.
24 E. M.	Min.*	1 by 1.5	0	+	+	0	O. P. D. only	Reactivation Pleural Effusion	A. W.
25 H. M. C.	Min.*	1 by 1	0	0	+	0	Rest, 6 months	Reactivation Pleural Effusion	A. W.
26 H. D. Mc C.	Min.	2 by 3	+	0	0	−	Rest, home	0	A. M. 3 Ch.
27 J. M.	Min.	1 by 2	+	0	0	0	Rest, 6 months	0	A. W.
28 E. M.	Pleurisy with Effusion		+	+	+	−	Rest, 6 months	0	A. W.
29 K. M.	Min.	1 by 2.5	+	0	0	+	Rest, 2 months San. O. R. A. A.	Reactivation	Under treatment
30 R. H. O.	M. A.	4 by 5 Cavity	+	+	+	+	Pneumothorax collapsed	0	Under treatment M. 3 Ch.
31 R. G. O'R.	Min.	2 by 3	0	0	0	0	O. P. D. only	0	A. M. 1 Ch.
32 M. R.	Min.	2 by 2.5	0	0	0	0	Rest, 6 weeks	0	A. W.
33 M. R.	F. A.	1.5 by 2	++	+	++	++	Pneumothorax, bilateral	Progression	Died
34 P. S.	Min.	L. U. L.	+	0	0	0	Rest, 12 months	0	A.
35 A. M. S.	Min.	2.5 by 2.5	+	+	+	−	Pneumothorax Re-expansion 1948	Reactivation	A. M. 1 Ch.
36 H. S.	Pleurisy with Effusion		±	0	+	0	O. P. D. plus rest	Reactivation A. S.	A. W.
37 C. I. S.	Min.	2 by 2	0	0		G. +	O. P. D. Pneumothorax Reexpansion	Reactivation	A. M. 1 Ch.
38 M. C. S.	Min.	1 by 2.5	0	0	0	0	O. P. D. only	0	A. M. 2 Ch.
39 T. T.	Min.	3 by 4	0	0	0	0	Rest, 6 months	0	A. W.
40 G. H. W.	Min.	2 by 1	0	+	0	0	Rest, 2 months	Reactivation Pleural effusion	A. M.
41 N. E. A.	Tuberculous adenitis		0	+	0	Biopsy proven	O. P. D. only	0	A. M.
42 F. B.	Min.	2.5 by 1.5	0	0	0	0	Rest, 3 months	0	A. W.
43 B. C. B.	Min.	1 by 1	0	0	0	0	Rest, 4 months	0	A. M. 3 Ch
44 C. O. B.	Min.	1.5 by 0.5	+	0	0	0	Rest, 5 months	0	A. M.
45 M. A. C.	Min.	1.5 by 2.0	+	0	+	0	Pneumothorax Re-expansion 1945	Reactivation A. S.	A. W.
46 G. S. C.	—	—	—	—	—	S. +	?	Rapid progression	Died—TB. M.

Table of Case Histories—Continued

CASE NUMBER	DIAGNOSIS	LESION SIZE IN CM.	SYMPTOMS		PHYSICAL SIGNS	BACILLI	TREATMENT	PROGRESSION REACTIVATION	END RESULT
			Constitutional	Local					
Initially positive reactors—Continued									
47 E. P. C.	M. A.	5 by 6 Pneumonic	+	+	+	G. +	Pneumothorax Bilateral re-expansion 1947	Progression ± 3 yrs.	A. M.
48 M. J. C.	M. A.*	Left lung	+	+	+	S. +	Thoracoplasty, left	Reactivation, Pleural effusion	A.
49 C. C.	Min.	2 by 3	+	+	+	−	Pneumothorax collapsed	Progression	Under treatment
50 M. C.	Min.	2.5 by 3	+	+	+	S. +	Rest, Sanatorium O. R. A. A.	Reactivation	Died hemorrhage
51 M. K. D.	Min.	1 by 3	+	+	0	S. +	Rest, 6 months Thoracoplasty	Reactivation	Under treatment M.
52 B. M. D.	Min.	2 by 3	0	0	0	0	Rest, 6 months	0	A. M. 2 Ch.
53 M. D.	M. A.	6 by 7	0	+	+	0	Rest, 4 months	0	A. W.
54 B. F.	Min.	1.5 by 1.5	0	0	0	0	Rest, 4.5 months	0	A. M
55 L. K. H.	Min.	1.5 by 3	0	0	0	0	O. P. D. only	0	A. M. 1 Ch.
56 A. C. H.	Min.	1.5 by 2	0	0	0	0	O. P. D. Pneuthorax	Reactivation	A. W. 1 Ch.
57 M. H.	M. A.	Bilateral apex	+	+	+	+	Sanatorium 6 years. Pneuthorax 6 years, Re-expansion, 1943	Progression	A. W.
58 J. K.	M. A.	R. L. L. Calc. ++	0	0	0	0	O. P. D. only	0	A. W. A. M.
59 H. K.	Min.	L. U. L. 2 by 3	+	+	+	0	Rest, 3 months	Reactivation Pleural effusion 1942 TB. Salpgts 1947	
60 G. S. L.	Min.	1.5 by 5.5	0	+	0	0	O. P. D. only	0	A. M. 1 Ch.
61 G. K. M.	Min.	6 by 8	+	+	+	−	Pneumothorax Re-expansion, 1946	Progression	A. M.
62 T. Mc.I.	M. A.	Right lung	+	+	+	S. +	Pneumothorax collapsed	0	Under treatment A. A.
63 A. McL. C.	Min.	Bilateral apical	+	+	−	−	Pneumothorax Re-expansion, 1946	0	A. M. 1 Ch.
64 M. R. M.	M. A.	7 by 11	+	0	0	−	Rest, eight months O. R. A. A.	0	A. M. 3 Ch.
65 I. G. O.	Min.	9 by 2.5	+	0	0	−	O. P. D. only	Reactivation	A. M. 1 Ch.
66 E. W. P.	Min.	1 by 1.5	0	0	0	0	O. P. D. only	0	A. M. 1 Ch.
67 R. A. P.	Min.*	1 by 2	+	+	+	−	Rest, 4 months	Reactivation Pleural effusion	A. W.
68 M. G. P.	Min.	1 by 1	0	0	0	0	O. P. D. only	0	A. M. 2 Ch.

Table of Case Histories—Concluded

CASE NUMBER	DIAGNOSIS	LESION SIZE IN CM.	SYMPTOMS		PHYSICAL SIGNS	BACILLI	TREATMENT	PROGRESSION REACTIVATION	END RESULT
			Constitutional	Local					
Initially positive reactors—Concluded									
69 M. St. G.	Min.	1.5 by 2.5	+	0	0	−	Pneumothorax Re-expansion 1948	Reactivation	A. W.
70 F. V.	Min.	1 by 2	+	0	0	0	Rest, 4 months	0	Under treatment
71 C. W.	Min.	2 by 2	+	0	0	−	Pneumothorax Re-expansion 1947	Progression	A.

Index

A. = Arrested.
M. = Married.
W. = Working.
O. P. D. = Out Patient Department follow-up only.
Rest = Rest treatment only.
Ch = No. of children.
* = With pleurisy with effusion.
O. R. A. A. = Own risk against advice (discharged).

THE PROBLEM OF TUBERCULOSIS CONTROL AMONG AMERICAN NEGROES[1,2]

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INTRODUCTION

The problem of tuberculosis control among United States minorities is difficult to discuss. Minorities do not exist here in a European sense. Economic, cultural, ethnic, and language barriers do not completely dissociate any group from the population as a whole. All types of tuberculosis may be found in all segments of the population without regard to ethnic origins or other outward characteristics which might distinguish individuals as members of special groups.

This discussion, therefore, will be concerned with trends in groups which are identifiable as different from the white majority on the basis of evident physical characteristics. The impossibility of making subtle scientific distinctions among individuals in gathering the basic data from which statistics are compiled imposes a practical limit upon our ability to draw fine conclusions. Considerations which affect the severity of tuberculosis among Negroes may be useful in planning the protection of the entire population.

THE NATURE OF THE PROBLEM

Death rates: In the United States registration area in 1910 the death rate from tuberculosis among the white population was 148.3 per 100,000 and among the Negro population the rate was 447.7 per 100,000. In 1945, after 35 years, the U. S. Public Health Service reports a rate of 32.7 per 100,000 for whites and 98.0 for Negroes. The ratio of white to Negro death rates remains at 1:3 despite the dramatic decline recorded for both groups. A greater disparity in death rates exists between 15 and 44 years of age where the Negro rate exceeds the white by five times (1).

The death rate for some other United States minorities is higher than that for the entire nation. Chinese, Japanese, Indian, Eskimo, Porto Rican, and Mexican-American rates are reported to be high (2).

The proportionate mortality from tuberculosis in major cities for 1945 shows the largest disparity between white and non-white deaths in the 15 to 24 year age groups. The severity of tuberculosis for non-whites appears to increase with the size of cities. The tuberculosis proportionate mortality is highest in Northern industrial cities (3).

The prevalence of pulmonary tuberculosis: The prevalence of tuberculous disease among Negroes *does not exceed* that among whites to an extent comparable

[1] From the Division of Chronic Pulmonary Diseases, Howard University School of Medicine, Washington, D. C.

[2] Presented before the Southern Tuberculosis Conference in Savannah, Georgia, October 2, 1948.

to the excess of mortality. Some surveys have actually shown a *smaller prevalence* of tuberculosis among Negroes even though the *death rate* exceeded that for whites by six or more times. Edwards reports this in his exhaustive report of mass surveys in Harlem (4). Comparable observations are reported by other observers (5, 6).

We are, therefore, confronted with the fact that pulmonary tuberculosis, while not more prevalent among American Negroes than among whites, is a more severe and more rapidly fatal disease. This has been confirmed in numerous studies (1, 7, 8, 4, 9).

The extent of infection: The extent of infection by tubercle bacilli in terms of the relative percentages of tuberculin-positive persons in non-white and white groups in the various localities is of importance here. New York City figures reported by Drolet in 1934 were 47.9 per cent positive tuberculin tests in young Negroes below age 15 and 52.1 per cent positives for young whites of a similar age. Death rates, however, were 10 times as high for this group of Negroes as for whites (10). A similar finding, although infection was more prevalent, was reported from the Phipps Institute in 1928 for South Philadelphia high school children (11). Whitney and McGaffrey reported a national prevalence of positive tuberculin reactions for whites of 46.5 per cent and 47.8 per cent for Negroes. Whites experienced a one per cent per year of age average increase in reactors and Negroes an increase of 0.5 per cent. The increase before age 20 was *more rapid* for Negroes.

Although approximately equal percentages of tuberculin sensitivity have been indicated for the white and non-white groups in many studies, it is possible that infection falls with different emphasis upon the non-white groups. A more rapid increase in positive reactors in the younger age groups in Negroes has been mentioned. Furcolow and others report a great disparity between positive reactors in Negro and white school children in Kansas City which would indicate that in this city, at least, Negro children below 18 are more frequently infected with tubercle bacilli than whites (12).

Although further studies are required at present, it may be assumed that the annual incidence of tuberculous infection is greater for Negroes below age twenty.

The concept of race: Differences in recorded vital and morbidity statistics have given rise to many theories concerning the influence of race-specific factors upon the severity of tuberculosis. This concept requires clear analysis. In a scientific sense, the Negro minority in the United States is not an ethnic entity (13, p. 136). The Negro is identified by skin color, other physical characteristics, or by descent from persons of African stock. These characteristics identify Negroes in the statistics of human welfare. The same factors set Negroes apart from the white majority in the cultural, economic, occupational, educational, and political life of all sections of this country. Such differences are not biological. It is, therefore, exceedingly difficult to base scientific conclusions concerning tuberculosis upon the common designation of race.

The variable factors which operate upon the non-white minority in contrast to the white would have to be strictly controlled in order to observe the single

and distinct influence of the predominant racial stock upon the tuberculosis epidemic.

The decline of the Negro tuberculosis death rate to less than 25 per cent of that for 1900 is difficult to explain as the operation of an inheritable disease-resisting factor. That the white death rate is now 16 per cent of that for 1900 does not imply the special operation of a factor linked to race. The differences in rate of decline may result from the influence of the peculiar economic, occupational, and cultural structure of American society.

If a racial or genotypic factor be eliminated as the sole reason for the differences in response to tuberculosis between whites and Negroes, we may hope for a solution in practical measures.

Epidemiologic and immunologic considerations: The observation that tuberculosis of the lung is a more severe disease in the non-white minority demands interpretation. If the explanation is to be found in the physical and environmental factors, these should bear with peculiar emphasis upon the Negro. Some whites should also be affected in proportion to the operation of adverse influences upon them.

Rich (14) has stated that the extent and destructiveness of a lesion which will develop in a given tissue within definite time after inoculation is increased by the virulence and number of bacilli.

The effect of this inoculum is also enhanced by the hypersensitivity of the host organism.

The destructive effects of these factors are modified by resistance which is both native and acquired. This relationship is expressed in quasi-mathematical form as:

$$L \text{ is equivalent to } \frac{V \times N \times H}{R(n + a)}$$

Influences which tend to increase the effect of the numerator in this expression would, therefore, increase the severity of the lesions. Influences which diminish the effects of the denominator would act similarly. Since lesions are admittedly severe among the non-white minority, some factors on the right of this expression must, therefore, operate with peculiar severity among non-whites and not to such a large extent among whites.

The virulence and number of bacilli: Since the bacilli causing pulmonary tuberculosis in this country are not confined to the majority or minority by physical barriers, their virulence can be assumed to be the same for all groups.

The number of bacilli involves: (a) a large single inoculum occurring as the result of a single exposure; (b) repeated inoculations in several exposures over a period of time.

Do these factors operate with greater severity among non-whites?

A group not generally educated to sanitary and hygienic practices may experience inoculation with larger numbers of tubercle bacilli with greater frequency than a better trained group. Conceivably, the more customary communal use of personal articles, a carelessness about personal contacts, and ignorance of the

dangers of contagion may lead to the more frequent infection of the non-white minority with large bacillary inocula.

Sterner Associates tabulate findings of the Federal Housing Administration which are shown in part in table 1.

These studies indicate substandard sanitation for a significantly greater proportion of Negro families in all areas of the country. The extent of overcrowding is severe for Negroes and much greater than for whites. In Detroit, for instance, 1.6 per cent of all dwelling units reported occupied by Negroes housed more than two persons per room against 0.4 per cent of the dwellings occupied by whites. The report also indicates that in urban areas in 1930, 29 per cent of Negro families had lodgers as against only 10 per cent of white families. The propor-

TABLE 1

Comparison of Housing Facilities for Whites and Negroes

CITY	YEAR OF STUDY	PERCENTAGE OF DWELLING UNITS IN NEED OF MAJOR REPAIR OR UNFIT FOR USE	
		Negro	White
Hartford, Conn.	1939	29.9	2.5
Buffalo, N. Y.	1939	36.2	8.9
Philadelphia, Pa.	1939	22.9	3.5
Harrisburg, Pa.	1939	72.8	12.6
Detroit, Mich.	1939	33.7	6.8
Alexandria, Va.	1936	66.5	14.8
Birmingham, Ala.	1939–1940	56.5	19.7
New Orleans, La.	1939–1940	46.8	14.1
Atlanta, Ga.	1939	59.2	21.6

tion of broken families was reported as approximately 10 per cent higher for Negroes than for native whites (15).

Poor housing, overcrowding, and their associated social and economic stresses operate with unique severity upon the Negro. Is it not conceivable that these conditions added to the other consequences of a low living standard may operate to increase the number and frequency of inoculations with tubercle bacilli for a larger proportion of Negroes?

The frequency of large inocula in the early decades of life may result from poor physical conditions of existence, a slower acquisition of the principles of hygienic living, and possibly from traditional employment in personal service capacities. The occurrence of rapidly progressive disease is, in itself, presumptive evidence of more intensive exposure to tubercle bacilli (16).

That family or household contact is less frequently detected among Negroes with tuberculosis points to heavy extra-domiciliary exposure. Whites may experience a larger number of slight casual contacts to account for the presence of infection when observed.

Hypersensitivity to the tubercle bacillus is difficult to measure. Work done at Phipps Institute suggests that Negroes react more frequently to the smallest

dose of PPD tuberculin and that the frequency of severe reactions is greater. At Howard University some 630 positive tuberculin reactors were found prior to 1940. Of these, 75 per cent reacted to the first dose of PPD (17).

A direct relationship appears to exist between numbers of bacilli inoculated and the severity of anaphylactic sensitization. Hypersensitivity is, therefore, increased with the number of bacilli and with greater frequency of inoculation. If Negroes experience larger and more frequent bacillary inocula, we may then account in large part for a greater degree of hypersensitivity.

The observed decrease in tuberculosis death rates in this country has accompanied an improvement in the physical conditions of living, in sanitation, in knowledge of hygiene, and in conditions of work. Minority groups have enjoyed these improvements to an appreciably lesser extent than the majority and consequently tend to experience more intensive exposure at earlier ages.

The slighter inoculation of bacilli among the majority resulting from less intensive exposure tends to produce active immunity or slowly progressive lesions when they occur. The more intensive inoculation in the non-white group produces progressive tuberculosis earlier in life or leaves foci which produce progressive disease in later life.

Resistance: Resistance to tuberculosis is a complex factor. It is not a measurable quantity. Its presence must be inferred from the reactions of tissues and organs to infection. It is a variable which may be lessened by any number of transient or persistent influences. Some of these factors may exert large general effects and so must be considered.

Species or racial resistance: Immunity is postulated upon the basis of observed tissue responses in experimental animals of many species and strains. Comparison of these pathological changes has been the basis for rating human individuals as resistant or susceptible. This analogy is accurate within limits. The conditions under which human infection may occur can hardly be duplicated for animals. The differences between human ethnic groups are not analogous to those between different species such as white mice and guinea pigs. The familial immune traits demonstrated to exist in rabbit families may exist in humans (18). We can safely assume, however, that a great many years would pass before humans could significantly "breed out" a comparable genetic trait which controls lack of resistance to tuberculosis.

Bogen (19) reports that the death rate from tuberculosis among Australians has been the lowest in the world since records have been kept. These people left England originally during a period of high death rates when racial immunity, if it existed, would be thought low. Americans migrating from England about the same time experienced extremely high death rates. The Australians have enjoyed favorable death rates, however, despite a low bed-to-death ratio. Since they have not lost large portions of population from tuberculosis, the killing off of susceptible strains cannot be presumed to account for the present favorable rates.

That there is native resistance to tuberculosis cannot be denied. That this resistance is linked directly to ethnic traits or that it has been influenced by

natural selection in our present society is not proved. Large scale deficiencies in the resistance to tuberculosis of non-white minorities cannot yet be scientifically explained as a race-specific phenomenon.

The influence of age: Resistance to progressive tuberculosis is a characteristic which appears to increase with age. Nevertheless, Chadwick (20) quotes Frost as pointing out that the group aged 50 to 60 in 1930, if followed back to birth, actually experienced the highest mortality at ages 20 to 30 and that the high rates at the older ages are the residuals of higher rates in early life.

Pinner (21, p. 499) stated, however, on the basis of autoptic experience, that the proportion of lethal or severe tuberculosis to total tuberculosis appears to decrease with age. This observation may be confirmed in any large scale chest roentgenogram survey by a comparison of the incidence of symptomatic active lesions per thousand to the proportion of total reinfection infiltrates in the various age groups examined. In Howard University students, the ratio of progressive reinfection lesions to total lesions has been thought a significant guide to show sex and age probability of progression (22). This ratio, if it can be applied, may supply concrete evidence of age-specific resistance to tuberculous progression. Since infection with large inocula may appear earlier in minorities, the importance of developing such an index is obvious.

Resistance varies with a number of physiologic phenomena associated with sexual maturation, childbearing, and other developmental and aging factors. These influences would seem to be equally influential in all groups and would assume added importance in a minority only when operative at an age during which heavy exposure is frequent.

Nutrition: Resistance to progressive tuberculosis appears to vary with the standard of living of the individual or groups (23). This is a complex influence in which many subfactors may operate. Of these, poor nutrition seems most important. The influence of nutrition upon the various elements of the population is inadequately studied. No extensive body of evidence is available to show the influence of deficient nutrition during the period of most active growth upon the ability to develop and maintain resistance to tuberculosis in later life.

The effect of extreme malnutrition upon tuberculous disease in concentration camp inmates in Germany appears to produce autoptic appearances similar to those reported by Pinner and Kasper in Negroes (24). A large incidence of lymphogenous and blood-borne tuberculous metastases and remarkably severe liver damage is reported (25).

Faber reported from Denmark in 1938 that low protein nutrition was one of the factors accounting for the spectacular increase in tuberculosis in the first world war (26). Pinner states that no other nutritional factor plays such a decisive role as protein in influencing the epidemic behavior of tuberculosis (21, p. 520).

Poor nutrition operates especially among Negroes. Myrdal states, upon the basis of 1941 Department of Agriculture studies, that "the majority of the Negro population suffers from severe malnutrition" (13, p. 375). This he attributes in part to poverty and in part to "cultural factors" influencing the

choice of foods. The influence of diet upon resistance to tuberculosis is obvious, especially since costly protein is one of the notoriously deficient items reported in the dietary.

War, metabolic diseases, and intercurrent infections would appear to act equally upon resistance in all groups and to exert no special influence upon the problem at hand.

Acquired resistance: Koch demonstrated that the inoculation of previously healthy animals with a pure culture of tubercle bacilli excited, after ten to fourteen days, a changed reactivity which was accompanied by the development of an immune reaction which reached its optimum in four to six weeks. The development of this immune reaction, however, depends upon the size of the initial inoculum and upon the frequency of inoculation in the ten to fourteen day preallergic phase. If the inoculum is large or frequently repeated, the allergic phase develops but progressive tuberculosis occurs, denoting an overwhelming of the host prior to the development of the immune response.

Holm has noted a comparable phenomenon in the natives of Bornholm, Denmark who, being largely tuberculin-negative, develop progressive tuberculosis when they migrate to the urban Danish mainland. Ferguson reports a similar situation among tuberculin-negative native white nurses exposed to open tuberculosis in Canadian hospitals.

Massive inoculation with human tubercle bacilli may result either in immediately progressive disease or in the development of foci which progress to an extent depending upon the speed with which resistance or acquired immunity develops.

The speed of fission of bacilli in large inocula may be assumed to exceed the speed of development of immunity which may at any point modify the resulting lesion to varying degrees of chronicity (27). Casual or slight exposure later in life, however, seems far more likely to produce an immune reaction which inhibits progression of the primary inoculum or its satellites and may impose chronicity or healing upon these or subsequent inocula

The protection of experimental animals by small inocula of tubercle bacilli has been demonstrated by many workers. The controlled administration of small amounts of avirulent tubercle bacillus has been demonstrated to cause the development of acquired immunity. The occurrence of small inocula of virulent bacilli might be responsible for the development of relative immunity among United States whites. Large inoculations with virulent bacilli are expected to occur more frequently in Negroes. Acquired immunity should develop more effectively in the less intensely exposed group.

WHAT NEEDS TO BE DONE FOR TUBERCULOSIS CONTROL AMONG THE NEGRO POPULATION

Known factors increase the severity of tuberculous disease among the Negro population in the United States. No special or unusual influences need be postulated to account for higher death rates. The thorough application of familiar community tuberculosis control programs to the entire population is of the

greatest urgency. The official and voluntary health organizations must enlist the participation of everyone.

The problem of tuberculosis among Negroes cannot be isolated in our thinking or planning. Emphasis should be placed on some special aspects of this problem.

1. *Research:* A program of research should be planned in order to study and identify the environmental, cultural, economic, and educational factors which may adversely influence the resistance of Negro Americans to tuberculosis. The program should include the following features:

(a) Modern methods of social research should be employed by trained social scientists to identify these environmental factors. Objective medical study should then be able to demonstrate statistically significant, physiologic, or pathologic variants produced by social and economic influences.
(b) Up-to-date information concerning the prevalence of tuberculous infection is needed. This should be specified for age, race, sex, and locality.
(c) Age-specific ratios between the incidence of frankly active pulmonary tuberculosis and that of all forms of pulmonary tuberculosis should be formulated from the largest possible chest roentgenogram survey experiences in each community. These ratios may be expected to indicate the age-specific expectancy of progressive tuberculosis for all elements of the population.

2. *Improved medical care:* The more rapid progression of pulmonary tuberculosis in the non-white makes it imperative that minor pulmonary infiltrates and early minimal tuberculosis be treated more effectively and vigorously by every medical and surgical means at our disposal.

The prevention of contagion by the earliest possible recognition and treatment of progressive disease is a medical and public health obligation which is obviously of particular importance.

3. *Isolation of open cases:* The early and effective isolation of "tubercle bacillus" carriers is necessary in *all groups* of our population. A program of good medical care should motivate the individual acceptance of isolation with a hope for recovery.

4. *Economic provisions for the tuberculous:* Early hospitalization, medical care, and isolation should be made possible by two strong steps:

(a) The means test should be abolished as a requirement for tuberculosis hospital treatment. No citizen should be *forced* to expend savings in order to undergo treatment for the general good of the community.
(b) Adequate financial assistance should be given to the families of tuberculous breadwinners during hospital treatment and convalescence. This would bring tuberculosis patients in marginal economic groups under earlier medical care and result in shorter hospitalization and earlier return to work.

5. *Educational improvement:* Every educational channel available should be devoted to the ideal of educating all Americans to the best standards of living, of hygienic practice, of nutrition, and of conditions of work. The general adoption of such standards will speed the acquisition of the cultural traits required to counteract the effects which reduce resistance.

A more general understanding of the harmful effects of urban and rural slums

upon national health will, it is hoped, lead eventually to intelligent attacks upon these problems.

6. *BCG vaccination:* BCG vaccination offers hope of developing a useful degree of acquired resistance in the younger age groups of the Negro population. The complexity of the factors producing increased susceptibility to progressive tuberculosis makes it imperative that we do not rely on this measure alone.

7. *Ancillary medical procedures:* The fullest possible assistance in the measures outlined above must be sought from the techniques of medical social work, public health nursing, vocational rehabilitation, and voluntary tuberculosis agencies. These services are essential to the support of the prophylactic and therapeutic programs. Their general adoption must be supported.

SUMMARY

1. Tuberculosis is a more severe disease among the non-white minority in the United States than for the majority.

2. The factor of race in the ethnic sense plays only a small part in identifying the Negro in the United States. Cultural, occupational, economic, and educational limitations set the non-white group apart. A biological explanation of the observed severity of tuberculosis in a group not biologically defined is not consistent with logic.

3. Environmental conditions increase the severity with which tuberculosis strikes. The number and severity of bacillary inocula are greater for a group which experiences to a greater extent than another the disadvantages of crowding, unsanitary environment, and social disorganization.

Hypersensitivity develops more strongly as a consequence of larger inocula with more bacilli. Resistance of the natural type depends on good nutrition and age of first intensive exposure. These two factors are demonstrably unfavorable to the maintainance of resistance in a large portion of the Negro minority. Acquired resistance develops following an inoculation with tubercle bacilli in an optimum dose. Massive or frequent inocula may cause hypersensitivity and, on a purely mathematical basis, may enable bacillary growth to outstrip the development of acquired immunity. This favors the development of progressive tuberculosis.

These factors are susceptible of demonstration and do not require the invocation of race-specific phenomena as speculative influences. Research to determine the specific physiologic consequences of environmental and nutritional deficiencies is much needed.

SUMARIO

El Problema de la Lucha Antituberculosa en las Minorías de los Estados Unidos

1. La tuberculosis es una enfermedad más grave entre las minorías no blancas de los Estados Unidos que que entre la mayoría de la población.

2. El factor raza en su sentido étnico sólo desempeña un pequeño papel en lo tocante a definir el estado de la minoría que no pertenece a la raza blanca, que queda también separada del resto de la población por limitaciones culturales,

vocacionales, económicas y educativas. Toda explicación biológica de la notoria gravedad de la tuberculosis en un grupo biológicamente indefinido resulta ilógica.

3. Las condiciones del medio acrecientan claramente la intensidad con que hiere la tuberculosis. Las que concebiblemente intervienen en una gran proporción de las minorías son:

(a) La cantidad y la gravedad de los inóculos bacilares son mayores en un grupo que experimenta en mayor grado que otro, las desventajas creadas por el hacinamiento, la insalubridad y la desorganización social.

(b) La hipersensibilidad se desarrolla más poderosamente a consecuencia de inóculos ma ores con más bacilos.

(c) La resistencia de tipo natural depende, entre otras cosas, de la nutrición y de la edad al tener lugar la exposición. Esos dos factores son notoriamente adversos al mantenimiento de la resistencia en una gran proporción de la minoría negra.

(d) La resistencia adquirida se desarrolla consecutivamente a la inoculación de bacilos tuberculosos en dosis óptima. El exceso o la frecuencia de los inóculos pueden provocar hipersensibilidad, pero a base puramente matemática, pueden hacer que la proliferación bacilar rezague el desarrollo de la inmunidad adquirida. Esta situación favorece la aparición de tuberculosis progresiva.

(e) Postúlase, pues, que la lesión tuberculosa será más grave en la población negra por hallarse una proporción mayor de ese grupo expuesta a la inoculación masiva, y por lo tanto al desarrollo de hipersensibilidad. Los factores del medio ambiente contribuyen a esa situación. Postúlase también que la resistencia natural de una gran proporción de los negros será baja debido al mal estado de su nutrición y a su exposición a una edad menor a la dolencia. La resistencia adquirida no se manifiesta tan rápidamente en la minoría por agobiar la intensidad de la exposición el organismo antes de que aquella pueda ocurrir.

Estos factores son susceptibles de demostración y no requieren la invocación de fenómenos etnoespecíficos como causas hipotéticas. Hay mucha necesidad de estudios que determinen las específicas consecuencias fisiológicas de las deficiencias del medio ambiente y de la nutrición.

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STREPTOMYCIN THERAPY OF TUBERCULOUS PNEUMONIA IN NEGRO ADULTS[1]

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INTRODUCTION

Tuberculous pneumonia is considered a major indication for streptomycin therapy (1). This extensive, exudative type of pulmonary tuberculosis is seen in its most malignant form in Negroes, and was an almost universally fatal condition prior to the advent of streptomycin. The present report is a description of the results obtained in the 15 Negro adults with tuberculous pneumonia who were treated with streptomycin on the Stanford Service of the San Francisco Hospital from 1946 to 1949. Much has been learned from these cases about the management of tuberculous pneumonia, and it is felt that application of the principles which have emerged from this study should produce more favorable results in the future.

OUTLINE OF THE STUDY

The Negro adults included in this study varied in age from 18 to 45; 8 were women, and 7 men. All were hospitalized during streptomycin therapy and were kept on bed rest except for bathroom privileges. Because of the serious nature of the illness, the patients remained in the hospital for considerable periods following cessation of antimicrobial therapy. Streptomycin was administered for two to four months in doses of 1.0 Gm. daily, which was usually given in two injections at twelve hour intervals. Other measures, including various forms of collapse therapy and other surgical procedures, were performed as they seemed indicated before, during, or after streptomycin therapy.

The diagnosis of tuberculous pneumonia was made on the basis of extensive, confluent, exudative pulmonary disease in patients manifesting considerable fever and toxicity. Posthemoptoic infiltrations, which cleared rapidly and were presumably caused by the aspiration of blood, were not included.

OBSERVATIONS AND RESULTS

Group 1. *Patients in whom there was improvement, followed by relapse:* In 11 of the 15 patients, there was an initial period of improvement, followed by relapse. As indicated in table 1, 4 of these patients are dead, and it is likely that most if not all of the remaining 7 will eventually succumb to the disease.

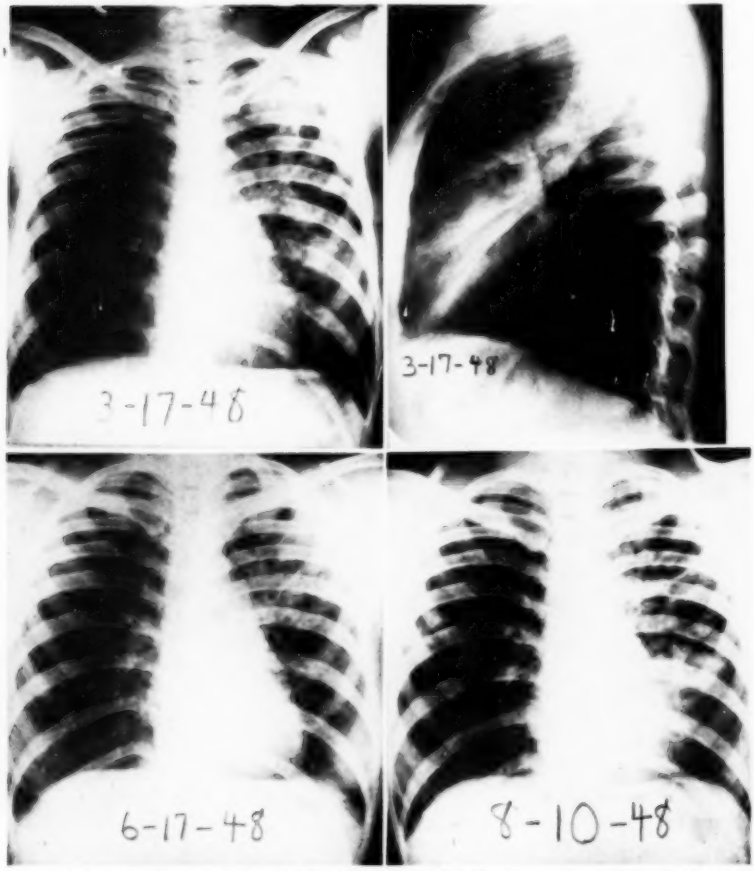
A typical example of the course of events occurring in this group is shown in figure 1. The patient was a 23 year old colored housewife who had been acutely ill with tuberculous pneumonia for two months prior to the administration of streptomycin. Symptomatic improvement was noted within a few days after starting therapy, and within two weeks the temperature, which had been rising to 102°F. daily, gradually returned to normal. During the two months of strepto-

[1] From the Department of Medicine, Stanford University School of Medicine, the Stanford Tuberculosis Service, San Francisco Hospital, and the San Francisco Department of Public Health.

TABLE 1

Results in 15 Negro Adults with Tuberculous Pneumonia Who Were Treated with Streptomycin

		NUMBER OF PATIENTS
Group 1	Improvement, followed by relapse Living 7 Dead 4	11
Group 2	Improvement, no relapse	4



FIGS. 1 A and B (Upper left and right). Patient A. B. Chest roentgenograms before treatment. Note the confluent exudative disease, located chiefly in the left upper lobe, clearly outlining the oblique fissure.

FIG. 1 C (Lower left). Film taken 10 days after end of two month course of streptomycin, showing some clearing of the parenchymal infiltrations. A large cavity is now visible in the left first interspace.

FIG. 1 D (Lower right). Enlargement of the cavity and progression of the disease on the left, with the appearance of infiltrations in the right fourth interspace. Patient died two months later.

mycin therapy she gained 10 pounds and her cough and sputum were greatly diminished. At the end of the treatment period, however, the sputum remained positive for tubercle bacilli and the organisms cultured were highly resistant to streptomycin. Because of the presence of cavitation in the left first interspace, a thoracoplasty was scheduled. Within two weeks after discontinuing streptomycin, however, her temperature again became elevated and her condition deteriorated so rapidly that the operation was never performed. Streptomycin was again started, but within five days she became almost totally deaf and the drug was discontinued. She died four months after completion of the first course of streptomycin therapy.

A similar case is illustrated in figure 2. This 45 year old, colored male had had cough, fever, and left chest pain for one month, during which he lost 30 pounds. During a three month course of streptomycin therapy he became afebrile and gained 15 pounds. Thoracoplasty was scheduled, but within two weeks after cessation of streptomycin his fever returned and he began to lose weight. Tubercle bacilli obtained at this time grew in the presence of 10 γ per cc. of streptomycin, but were inhibited by 100 γ. Streptomycin was given for a second two month course, but his condition grew steadily worse and he died two months after completion of the second course.

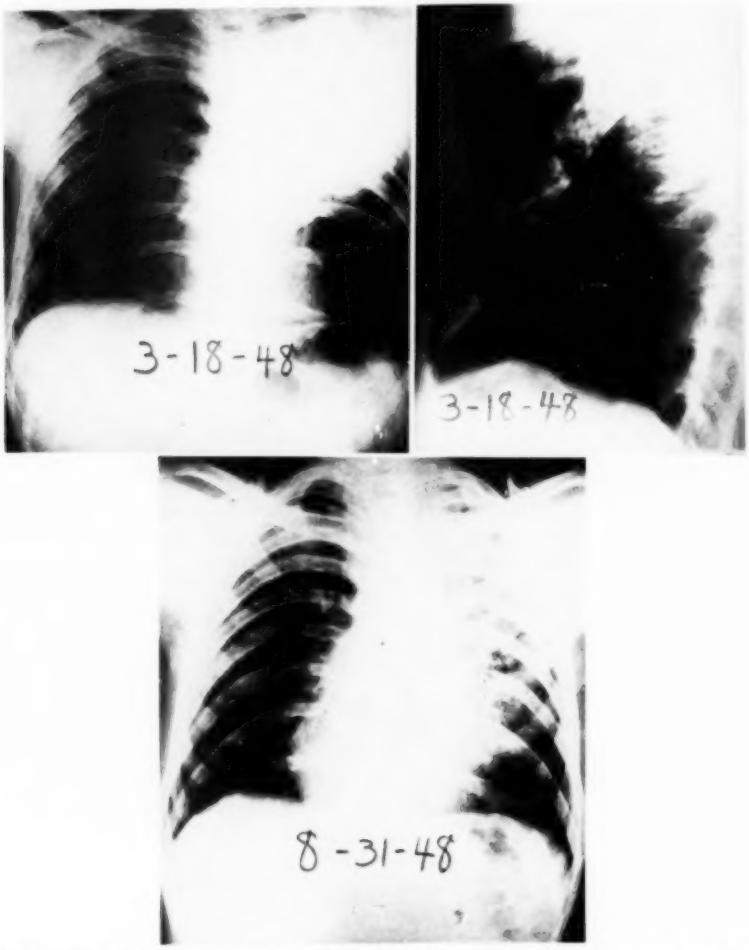
The chest roentgenograms of a third patient in this group are presented in figure 3. This 27 year old, colored male was thought to have a nontuberculous bacterial pneumonia in October 1946 on the basis of cough, sputum, right chest pain, and right upper lobe infiltration on the roentgenogram. He was treated by a private physician but failed to improve, and in April 1947 he was admitted to a nearby sanatorium with tuberculous pneumonia. He had lost 25 pounds and was very ill. Pneumoperitoneum was instituted and he received streptomycin for eleven weeks from July to September 1947. During this period he showed marked symptomatic improvement and gained 5 pounds, but his condition became worse almost immediately after antimicrobial therapy was discontinued. He was transferred to the San Francisco Hospital in January 1948 where pneumoperitoneum was continued, but the situation was obviously hopeless and the patient died four months later.

The course in the other 8 patients in this group was strikingly similar to that which occurred in these 3 patients. In 5, some form of collapse therapy was administered, but in every instance it was inadequate to control the disease. Three patients received both pneumothorax and pneumoperitoneum. One patient received a 2 stage thoracoplasty, but the cavities were not closed by this procedure and she is steadily getting worse.

Group 2. *Patients showing improvement, without relapse:* In contrast to the 11 patients in Group 1, the results in the 4 patients comprising Group 2 have been highly satisfactory to date. Since the objective of this study is to discover factors which are of importance in bringing about a favorable therapeutic result, these 4 cases will be presented briefly. Two received pneumoperitoneum in addition to streptomycin, and 2 had pneumonectomies.

One of the most striking responses occurred in a 26 year old male, whose

films are presented in figure 4. He had been ill for ten weeks prior to streptomycin therapy, with cough, sputum, fever, abdominal cramps, and diarrhea. His



FIGS. 2 A and B (Upper left and right). Patient S. H. Chest roentgenogram one week before starting streptomycin, showing extensive exudative disease with cavitation, confined chiefly to the left upper lobe.

FIG. 2 C (Lower). Film two months after the first course of streptomycin, showing spread and further excavation. The infecting organisms were resistant, and the patient pursued a progressively downhill course despite a second course of streptomycin therapy.

temperature, which was 104°F., fell to normal during the first month of treatment, the gastro-intestinal complaints disappeared, and he gained 30 pounds.

Pneumoperitoneum was started two weeks after completion of the ninety day course of streptomycin. Sputum and gastric cultures have been negative for

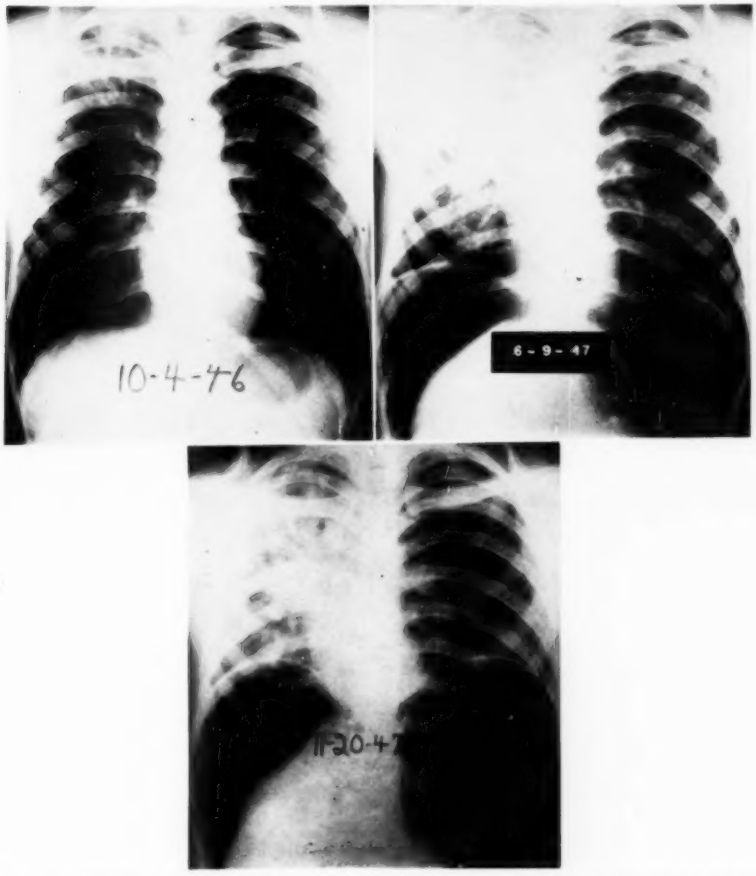


FIG. 3 A (Upper left). Patient E. P. Roentgenographic appearance at the time a diagnosis of "pneumonia" was made.

FIG. 3 B (Upper right). Condition a month after pneumoperitoneum was instituted, and three weeks before streptomycin was started. There is now an extensive tuberculous pneumonia of the right lung.

FIG. 3 C (Lower). Film taken two months after streptomycin was discontinued, showing progression of the disease with extensive cavitation. Death occurred six months later.

tubercle bacilli since the second month of streptomycin therapy. In view of the sudden onset, the bilaterally symmetrical chest lesions, the gastro-intestinal lesions, the prompt "conversion" of the sputum, and the lack of definite cavita-

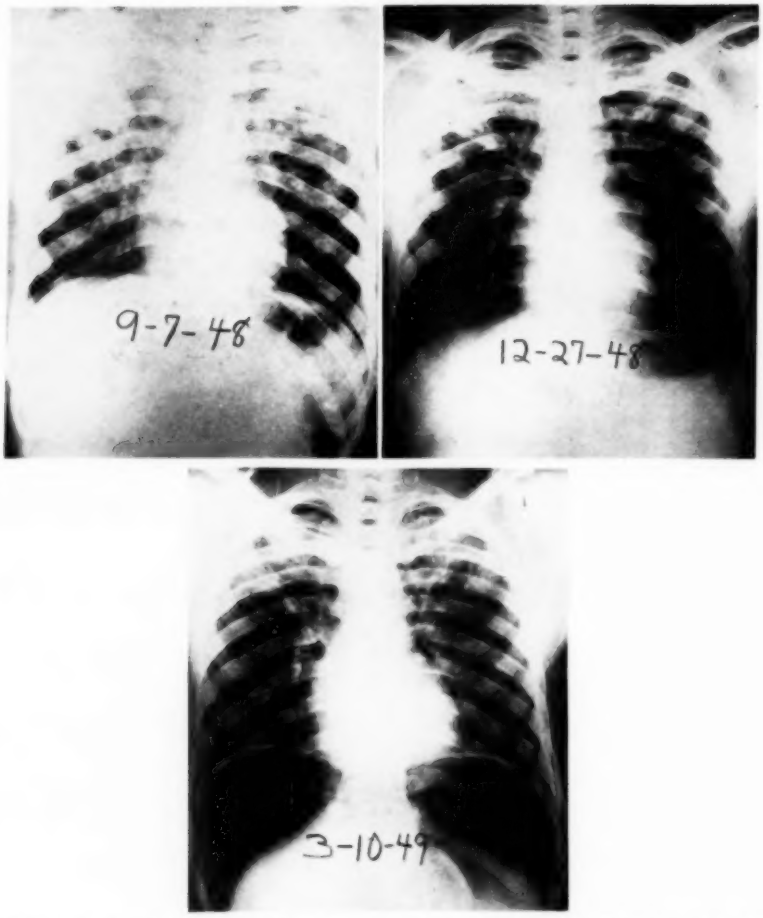


FIG. 4 A (Upper left). Patient E. H. Extensive bilateral exudative disease ten days before streptomycin was administered. This may have been hematogenous in origin.

FIG. 4 B (Upper right). Marked regression of the pulmonary infiltrations as seen eight days after the ninety day course of streptomycin therapy.

FIG. 4 C (Lower). Further regression is noted 2 months after starting pneumoperitoneum. In spite of the suggestive cavitation in both first anterior interspaces, sputum and gastric cultures have been repeatedly negative.

tion, it is possible that the disease in this case may have been hematogenous in origin. If so, the predominately interstitial character of the lesions may account in large part for the favorable response obtained.

The other patient who received pneumoperitoneum was a 22 year old house-

wife with a left lower lobe pneumonia which showed considerable progression during the first five weeks in the hospital, before streptomycin was administered (figure 5). A 3 cm. cavity, with a fluid level, could be faintly visualized above

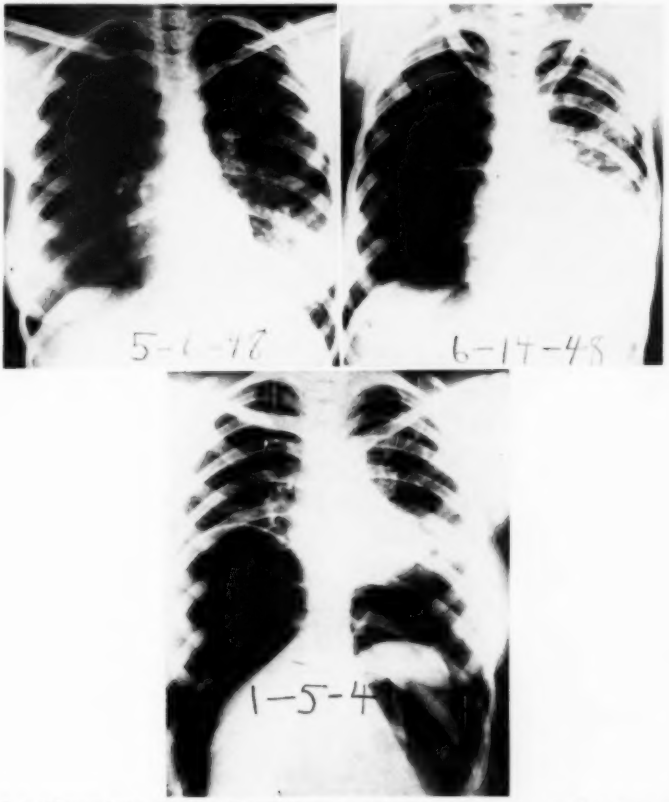


FIG. 5 A (Upper left). Patient L. W. Pneumonitis, left lower lobe, with a 3 cm. cavity just above the diaphragm.

Fig. 5 B (Upper right). Marked spread of the tuberculous pneumonia, left lower lobe, six weeks later and twelve days before streptomycin was started. Patient was quite toxic and febrile at this time.

FIG. 5 C (Lower). Film taken fourteen weeks after discontinuing streptomycin, and twelve weeks after starting pneumoperitoneum. There has been marked clearing of the pneumonia, and the cavity is apparently closed. Note the calcifications in the spleen.

the left diaphragm in the first film. Streptomycin was given in daily doses of 1.0 Gm. for ninety days, and two weeks later pneumoperitoneum was instituted. She gained 20 pounds and sputum and gastric washings became negative for tubercle bacilli during the second month of streptomycin therapy. Six months

following the completion of antimicrobial therapy, she is showing continued improvement, and the plan is to continue pneumoperitoneum for several years.

Two patients have recently been observed in whom a more aggressive approach seemed indicated. The first of these was an 18 year old housewife who was three months pregnant when she entered the hospital in September 1948,

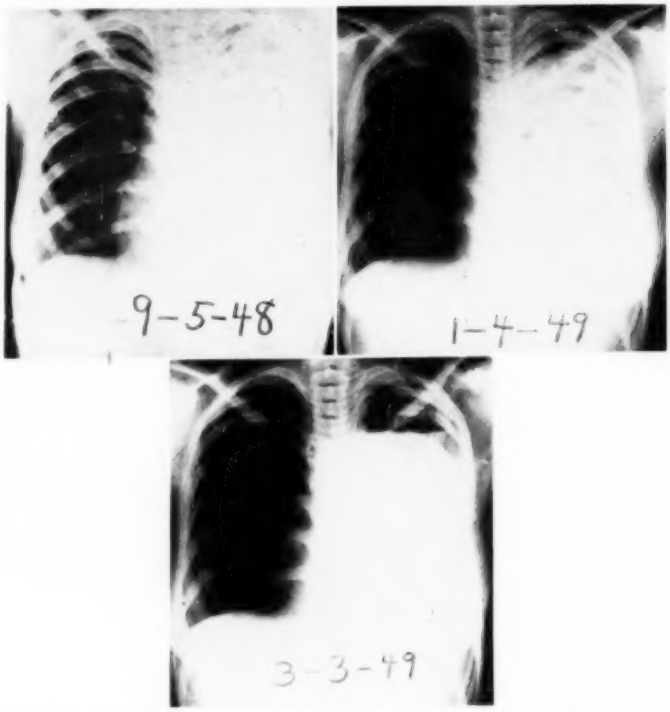


FIG. 6 A (Upper left). Patient B. S., with extensive involvement of the left lung. She was three monghs pregnant at this time.

FIG. 6 B (Upper right). Film taken ten days following completion of the first course of streptomycin, showing some clearing but extensive excavation.

FIG. 6 C (Lower). Appearance seven weeks after starting the second course of streptomycin, and five weeks following left pneumonectomy.

with an extensive tuberculous pneumonia of the left lung (figure 6). Although she had a daily temperature elevation to 102°F. or higher and had lost 15 pounds, she showed a surprising lack of awareness of her symptoms. She was placed on streptomycin September 30, 1948, and two days later the pregnancy was interrupted by abdominal hysterotomy. There was a weight gain of 13 pounds during three months of streptomycin therapy, but at the end of treatment she still had a daily fever of 99.5°F. Realizing that her course without further treatment

would be like that of the cases in Group 1, a second course of streptomycin was started January 19, 1949, and left pneumonectomy was performed January 29,

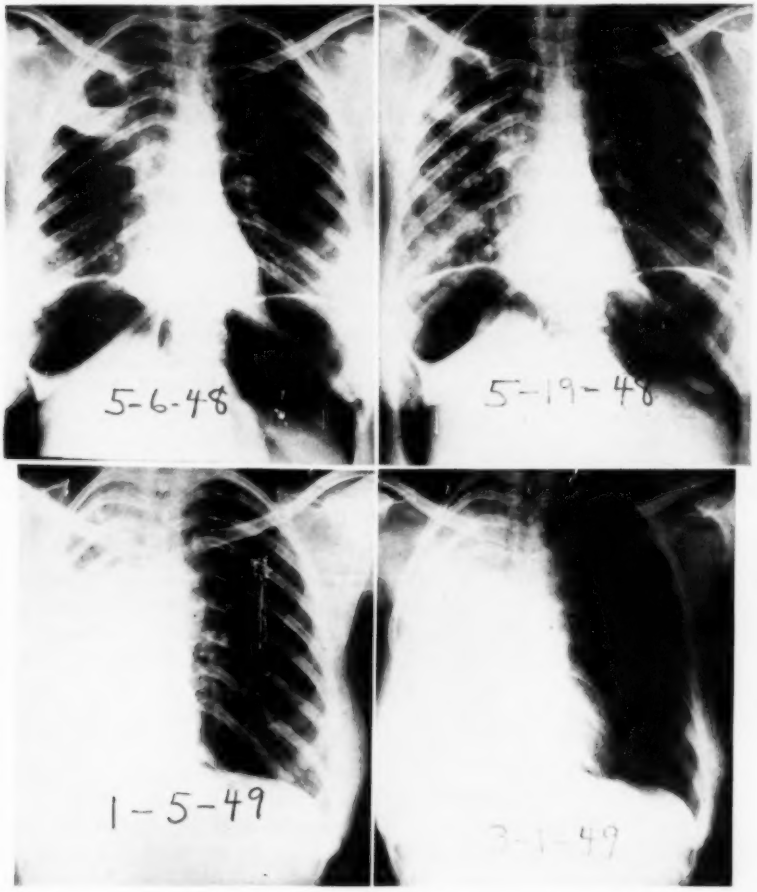


FIG. 7 A (Upper left). Patient M. E. Right upper lobe cavity of seven months duration with a fluid level present.

FIG. 7 B (Upper right). Infiltration throughout the right lung four days after the sudden emptying of the cavity contents into the right bronchial tree.

FIG. 7 C (Lower left). Extensive tuberculous pneumonia, right lung, three weeks after starting streptomycin, and three days before right pneumonectomy.

FIG. 7 D. (Lower right). Film taken seven weeks after right pneumonectomy.

1949. The postoperative course was uncomplicated. At present, two months after the operation, she is afebrile, her sputum and gastric washings are negative

for tubercle bacilli on smear and culture, and she is gaining weight. She refuses thoracoplasty, but a permanent left phrenic interruption is scheduled. The follow-up period is too short to predict the eventual outcome, but the outlook so far is certainly favorable as compared with the first 11 patients. It is of particular interest that a sensitivity test started before the pneumonectomy, but reported a month after the operation, showed the organisms to be resistant to 1,000 γ of streptomycin per cc. of medium.

The second case was a 39 year old housewife who was found to have a tuberculous cavity of the right upper lobe in late 1947. By May of 1948, despite right pneumothorax and pneumoperitoneum, the cavity was still open and it contained a fluid level. On May 15, 1948, the cavity contents suddenly flowed into the right lung, causing an extensive spread of the disease. During the next six months she lost 35 pounds and ran a downhill, febrile course. Because her condition was considered desperate, streptomycin therapy was started December 16, 1948, and a right pneumonectomy was performed January 8, 1949. The postoperative course was stormy for two weeks, but since then she has been afebrile and two months after the operation has gained 5 pounds. Several sputum smears and gastric cultures, since surgery, have been negative for tubercle bacilli. She refuses thoracoplasty. Again, the follow-up period is very brief, but the situation seems encouraging and the condition certainly would have terminated fatally without surgery.

COMMENT

Certain general principles concerning the management of tuberculous pneumonia seem apparent in viewing the results obtained in this series. Beneficial effects of streptomycin were noted in every case, as manifested by marked symptomatic improvement, decline in fever, diminution of cough and sputum, and gain in weight. The improvement was only temporary, however, unless streptomycin therapy was combined with adequate collapse measures. The extensive, destructive nature of the disease, with its widespread tissue necrosis and cavitation, was such that streptomycin alone caused only temporary suppression of the process and relapse and progression followed within a few weeks. Similar experiences have been described by others (2).

Collapse therapy or other surgery was instituted in 12 patients, but in only 4 did it aid in controlling the disease. Artificial pneumothorax was attempted in 3 cases, but, in keeping with the usual experience in tuberculous pneumonia, it was unsuccessful. Pneumoperitoneum appeared to exert a beneficial effect in 2 cases (figures 4 and 5). In one of these a 3 cm. cavity overlying the left diaphragm was apparently closed, and in the other the sputum became negative for tubercle bacilli and cavitation was no longer demonstrable. Pneumoperitoneum was administered at some time to 9 patients, but the amount of collapse produced was not adequate to control the extensive exudative and cavitary disease. The one patient who received a thoracoplasty had several large cavities which were not closed by the procedure, and her condition has steadily deteriorated since the operation.

The 2 patients in whom pneumonectomies were performed had predominately unilateral disease of the sort which had invariably terminated fatally in previous cases. The follow-up period has been short, but the results so far are encouraging and it is felt that an aggressive approach is indicated in this type of case. It is possible that the patients shown in figures 1, 2, and 3 might all have been saved if lobectomies or pneumonectomies had been performed at a judicious time.

It is evident then that the aim should be to provide adequate collapse therapy or other surgical measures and that these must be appropriately timed in relation to the streptomycin therapy, and particularly to the development of streptomycin-resistant infections. Two patients in the present series relapsed following streptomycin before a scheduled thoracoplasty could be performed. Generalizations concerning the type of collapse are not warranted; each case must obviously be decided on its own merits. In a disease as malignant as tuberculous pneumonia in Negroes, it is too much to hope to salvage every case. It would appear, however, on the basis of what has been learned in this study, that thoughtful planning and careful timing should make it possible to increase appreciably the percentage of cases permanently benefited.

SUMMARY AND CONCLUSIONS

Sustained improvement has been noted in 4 of 15 Negro adults with tuberculous pneumonia treated with streptomycin; relapse occurred in the other 11 following an initial period of improvement. Properly timed, adequate collapse therapy or other surgical procedures appear to be essential adjuvants to streptomycin administration in bringing about permanent improvement in this form of pulmonary tuberculosis, which is so highly fatal in Negroes. The early postoperative course has been encouraging in 2 patients with predominately unilateral disease in whom pneumonectomies were performed.

SUMARIO Y CONCLUSIONES

Estreptomicinoterapia de la Neumonía Tuberculosa en Negros Adultos

En 4 de 15 negros adultos con neumonía tuberculosa tratada con estreptomicina notóse mejoría sostenida, en tanto que en los otros 11 un período inicial de mejoría fué seguido de recaída. Cronológicamente coordinados, la colapsoterapia adecuada u otros procedimientos quirúrgicos parecen ser coadyuvantes esenciales de la estreptomicinoterapia para obtener mejoría permanente en esta forma de la tuberculosis pulmonar, que es tan letal en los negros. En 2 enfermos con enfermedad de predominio unilateral en quienes se ejecutaron neumonectomías, la evolución postoperatoria temprana ha sido alentadora.

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THE EFFECT OF ANTIHISTAMINE MEDICATION ON THE TUBERCULIN REACTION IN CHILDREN[1]

ELI FRIEDMAN AND IRVING SILVERMAN

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INTRODUCTION

The literature of late has had several articles attesting to the effectiveness of antihistamine agents in partially or completely inhibiting histamine wheals, allergic wheals, and passive transfer wheals. Typical of such reports is one by Elias and McGavick (1), in which nonallergic patients were subjected to histamine skin tests before, during, and after oral administration of Benadryl. A definite diminution in both wheals and erythema was noted after three days of oral treatment with 100 mg. of the drug daily. Arbesman *et al.* (2) observed similar results using a dosage of 50 to 100 mg. of oral Pyribenzamine and skin testing with histamine or allergens (ragweed, timothy, et cetera) forty-five minutes later.

It is surprising that, despite the widespread interest in the effects of the antihistamine agents on allergic manifestation, very little has been reported on the effect of these drugs on so common a reaction as the tuberculin test which is generally regarded as allergic in nature. Boquet (3) tested the action of several antihistamine agents on the intradermal tuberculin reaction in guinea pigs and was unable to find any inhibiting effect. R. W. Sarber (4), on the other hand, reports positive results on the tuberculin reaction in guinea pigs. He administered Benadryl subcutaneously in a dosage of 50 mg. per Kg. to 30 guinea pigs in which tuberculin sensitivity had been induced by the intraperitoneal injection of a suspension of mixed human and bovine strain of tubercle bacilli. The conclusions reached by Sarber are that in adequate dosage levels Benadryl causes a reduction in the tuberculin skin reaction and markedly reduces the incidence of necrosis in guinea pigs. On the basis of these findings he states that it is important to determine whether an individual being tested is receiving any antihistamine compound at the time of tuberculin testing before correct interpretation of a negative reading can safely be made. A search of the literature failed to reveal any similar careful studies performed on humans.

In the present study observations have been made on the effect of orally administered Tripelennamine Hydrochloride (Pyribenzamine Hydrochloride-Ciba) on the tuberculin reaction in 43 children known to be positive reactors to tuberculin.

METHOD OF INVESTIGATION

The study was conducted at the Prendergast Preventorium for Children. The substance used for intradermal testing was old Tuberculin, supplied by the Massachusetts Department of Public Health. To avoid the possibility of severe

[1] From the Prendergast Preventorium, Boston, Massachusetts.

TABLE 1

Tuberculin Reaction (1:100,000) with and without Pyribenzamine

	WITHOUT PYRIBENZAMINE		WITH PYRIBENZAMINE 50 MG. DAILY FOR FOUR DAYS	
	Induration	Total erythema	Induration	Total erythema
	mm.	mm.	mm.	mm.
1. A. S.	12 by 12	33 by 22	14 by 14	12 by 26
2. D. M.	12 by 12			45 by 28
3. A. T.	20 by 20	35 by 48	15 by 18	32 by 44
4. R. H.	10 by 10	28 by 20	10 by 12	20 by 30
5. M. H.	12 by 17	24 by 44	14 by 17	30 by 42
6. K. S.	10 by 10	18 by 26	10 by 14	
7. L. W.	15 by 17	32 by 45	16 by 17	36 by 45
8. K. N.	10 by 10	40 by 15	15 by 16	45 by 40
9. R. D.	10 by 10	15 by 15	14 by 13	32 by 40
10. E. P.	10 by 10	25 by 28	10 by 10	23 by 23
11. D. W.	10 by 10	20 by 26	14 by 12	20 by 25
12. P. S.	9 by 10	15 by 20	12 by 13	20 by 28
13. E. B.	10 by 10	45 by 40	12 by 13	32 by 35
14. D. K.	8 by 9	22 by 30	11 by 12	40 by 45
15. B. M.	15 by 20	30 by 40	16 by 16	25 by 40
16. S. W.	10 by 15	30 by 50	10 by 10	23 by 26
17. J. G.	10 by 10	20 by 25	10 by 10	22 by 30
18. M. T.	10 by 10	44 by 25	14 by 14	30 by 38
19. R. D.	10 by 10	17 by 35	10 by 10	24 by 20
20. T. W.	15 by 15	30 by 48	12 by 15	40 by 44
21. B. N.	10 by 10	25 by 25	8 by 8	22 by 25
22. S. W.	15 by 15	40 by 55	8 by 8	
23. C. D.	10 by 10	22 by 30	10 by 10	22 by 25
24. D. W.	8 by 9	14 by 16	14 by 16	
25. T. D.	10 by 20	20 by 50	9 by 21	30 by 46
26. J. L.	7 by 10	20 by 27	6 by 6	
27. R. B.	8 by 6		14 by 15	36 by 45
28. V. B.		25 by 35	10 by 20	15 by 20
29. E. J.	15 by 13	26 by 35	13 by 14	35 by 38
30. P. D.	17 by 12	45 by 33	6 by 6	23 by 35
31. V. D.	12 by 17		14 by 12	
32. V. W.	10 by 12	15 by 22	10 by 12	25 by 40
33. P. S.	8 by 8	14 by 20	6 by 6	22 by 30
34. W. V.	10 by 10	22 by 26	12 by 13	30 by 34
35. M. S.	10 by 10	17 by 23	15 by 15	
36. R. D.	10 by 6		7 by 10	25 by 25
37. J. L.	14 by 16	22 by 35	8 by 8	
38. L. K.	10 by 5	18 by 30	12 by 12	25 by 36
39. C. B.		30 by 50		32 by 48
40. F. C.	10 by 15		15 by 20	
41. D. K.	10 by 8	28 by 50	14 by 17	
42. A. L.	8 by 10	20 by 15	10 by 10	
43. W. C.	10 by 12	20 by 27	12 by 13	25 by 28

reactions, and in an effort to obtain as nearly as possible threshold levels of tuberculin, a dilution of 1:100,000 (.001 mg.) was used. Forty-eight clear and definite reactions were read on the basis of the extent of induration and erythema after forty-eight hours.

Several days later 43 of the children, whose ages ranged between five and eleven years, were given Pyribenzamine in the dosage of 60 mg. daily for two days before the tuberculin test was repeated. After the test, the Pyribenzamine administration was continued in the same dosage for another two days, at which

TABLE 2

Controls without Pyribenzamine

	INDURATION	TOTAL ERYTHEMA	INDURATION	TOTAL ERYTHEMA
	mm.	mm.	mm.	mm.
1. N. L.	14 by 12	20 by 33	10 by 10	25 by 26
2. J. D.	10 by 10		7 by 10	26 by 32
3. F. M.	10 by 10	25 by 45	12 by 16	35 by 40
4. D. G.	18 by 25		10 by 11	24 by 34
5. J. P.	10 by 11	16 by 20		32 by 41

TABLE 3

Tuberculin (1:100,000) Reactions with and without Pyribenzamine

	WITHOUT PYRIBENZAMINE		WITH PYRIBENZAMINE 240 MG DAILY FOR FOUR DAYS	
	Induration	Total Erythema	Induration	Total Erythema
	mm.	mm.	mm.	mm.
1. J. G.	10 by 10	20 by 25	16 by 20	37 by 70
2. B. N.	10 by 10	25 by 25	14 by 16	30 by 38
3. C. D.	10 by 10	22 by 30	15 by 15	24 by 25
4. J. W.	10 by 12	15 by 22	20 by 24	30 by 40
5. G. K.	10 by 5	18 by 30	15 by 20	
6. D. K.	10 by 8	38 by 30	17 by 21	42 by 50
7. A. L.	8 by 10	20 by 15	12 by 17	
8. F. M.	10 by 10	25 by 45	15 by 16	35 by 40
9. D. G.	18 by 25		10 by 10	24 by 40
10. J. P.	10 by 11	16 by 20	14 by 22	35 by 50

time a second reading was made (table 1). The remaining 5 children were not given Pyribenzamine but were retested with the others to act as controls of the intensity of the tuberculin reaction itself (table 2).

At a later date, 10 of the above children were again studied using larger doses of Pyribenzamine (240 mg. daily for two days). They were retested with 1:100,000 tuberculin which was followed by two more days of Pyribenzamine in 240 mg. doses before final reading (table 3). Here again a group of 5 children were tested as controls without receiving the antihistamine agent (table 4).

RESULT

It may be seen from the data in tables 1, 2, 3, and 4 that Pyribenzamine, in the stated doses, had no inhibiting effect on tuberculin reactions in children. No toxic effects were noted from the medication. An interesting sidelight noted was that several of the children who received Pyribenzamine had marked relief from pruritus caused by insect bites and dermatitis venanata.

TABLE 4

Controls without Pyribenzamine

	INDURATION	TOTAL ERYTHEMA	INDURATION	TOTAL ERYTHEMA
	mm.	mm.	mm.	mm.
1. R. H.	10 by 10	28 by 20	12 by 10	30 by 32
2. K. S.	10 by 10	18 by 26	8 by 15	24 by 48
3. R. D.	10 by 10	40 by 25	15 by 16	30 by 50
4. K. N.	10 by 10	15 by 15	18 by 20	
5. D. W.	10 by 10	20 by 26	10 by 11	24 by 47

DISCUSSION

Although the various antihistamine drugs show considerable variation in their chemical structure, their therapeutic results, with the exception of side effects, are quite similar. It is probable, therefore, that these findings with the use of Pyribenzamine would have been repeated if any other antihistamine drug in the same comparative dosage had been used.

The fact that antihistamine drugs have no perceptible effect on the tuberculin skin test corroborates the views of Zinsser (5) on the nature of the allergic response involved in the development of the tuberculin skin tests. According to Zinsser there are two types of allergic responses on the part of the body to the tubercle bacillus and its products. One is an anaphylactic reaction, which is a protein reaction of the immediate edema-hypermia (wheal type). The other is a tuberculin type reaction caused by the bacterial organism resulting in a delayed inflammatory reaction, causing more profound damage to the tissues.

The anaphylactic type reaction, according to Lewis (6), is caused by a histamine-like substance which is freed at the site of a local allergic reaction as a result of cellular injury. This histamine-like substance then reacts on the tissues to produce a characteristic "triple response": local dilatation of the small vessels; increased permeability; and diffuse dilatation of nearby arterioles. The classic example of this phenomenon is the resulting wheal when a specific antigen is introduced into the skin of an allergic individual and this reaction is inhibited by antihistamines.

In the tuberculin type reaction, it is probable that histamine does not play an important role. It is usually, although not always, dependent on the presence of tuberculous infection, is independent of anaphylaxis, and from the present findings is not inhibited by antihistamine medication.

CONCLUSIONS

1. Pyribenzamine in an oral dose of 60 mg. daily for four days had no inhibiting effect on the tuberculin reaction of 43 children ranging in age from five to eleven years.

2. Pyribenzamine in an oral dose of 240 mg. daily for four days had no effect on the tuberculin reaction of 10 children.

3. In routine tuberculin testing one need not be concerned as to whether the patient is receiving Pyribenzamine, or any antihistamine medications, during the same period.

4. It is believed that the observations presented are in agreement with the belief that a basic difference exists between tuberculo-allergy and tuberculo-anaphylaxis.

CONCLUSIONES

Efecto de la Medicación Antihistamínica sobre la Reacción a la Tuberculina en los Niños

1. La piribenzamina, a dosis oral de 60 mg. diarios durante cuatro días, no ejerció efecto inhibidor sobre la reacción a la tuberculina en 43 niños de cinco a once años de edad.

2. La piribenzamina, a dosis oral de 240 mg. diarios durante cuatro días, no mostró efecto sobre la reacción a la tuberculina de 10 niños.

3. En la comprobación corriente con tuberculina, no hay que prestar atención a si el sujeto recibe o no piribenzamina u otra medicación antihistamínica durante el mismo período de tiempo.

4. Parece que los datos aquí ofrecidos confirman la creencia en una diferencia básica entre tuberculo-alergia y tuberculo-anafilaxia.

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CHEMOTHERAPY OF MURINE LEPROSY[1, 2]

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INTRODUCTION

The rapid development of chemotherapy in the past decade has stimulated renewed interest in the treatment of diseases caused by acid-fast organisms. Several of the recently developed therapeutic agents have been evaluated in leprosy, but few investigators have concerned themselves with therapy in experimental murine leprosy. Faget and his colleagues (1, 2) observed that human leprosy is benefited by treatment with either Promin or Diasone. Also Muir (3) reported favorable results from the use of Diasone. Few data are available on the therapeutic efficacy of the antibiotics. Penicillin was used unsuccessfully in the treatment of human leprosy by Faget and Pogge (4). The vagaries of Hansen's disease, however, make the evaluation of therapeutic agents difficult, and the chronicity of leprosy necessitates years of observation during which time many uncontrolled variables are introduced.

The need for an experimental animal to amass accurate data is urgent, but as yet no animal host has been found to be susceptible to *Mycobacterium leprae* of human origin. Murine and human leprosy are sufficiently similar, however, to consider possible the application of data from experimental chemotherapeutic studies of the murine infection to the disease in man. Although Fite (5) observed minor differences in the microscopic pathology of the two types of infection, it is still a matter of speculation whether they reflect differences in the host or the parasite. Few studies on the chemotherapy of murine leprosy have been carried out. A recent report by Cowdry and Ruangsiri (6), who employed Promin in the treatment of rats with well-developed leprous nodules, concluded that it had "no consistent effect" on the histologic structure of the lesion, although the general health of the animals was improved. Because of the paucity of data on the evaluation of recently developed therapeutic agents in murine leprosy and their possible use in human leprosy, the present investigation was undertaken to compare the therapeutic efficacy of Promin, Diasone, penicillin, and streptomycin, employing dosages equivalent to those recommended in man.

MATERIALS AND METHODS

Two strains of murine leprosy were employed in the experiments. One strain, which has been carried through several passages in white rats in the laboratories of the Department of Bacteriology of the University of Rochester School of Medicine and Dentistry, was obtained

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from Krakower and Gonzalez (7) who recovered it from a mouse caught at the School of Tropical Medicine, San Juan, Puerto Rico. The other strain was supplied by Sellards of Harvard University approximately ten years ago and has been in experimental use ever since.

The inoculum was prepared from a subcutaneous leproma removed aseptically, placed in a sterile mortar, minced with scissors, and ground with alundum. Sufficient 0.85 per cent sodium chloride solution was added to obtain approximately a 20 per cent suspension. Films were then prepared from the suspension, stained, and observed to determine the relative number of acid-fast organisms.

Groups of from 10 to 20 white rats, Wistar strain, not over 3 months of age and weighing from 150 to 200 Gm., were inoculated subcutaneously with 0.2 ml. of the suspension rich in acid-fast bacilli. The usual site of injection was in the region of the right precrural lymph node. In each experiment a group of 5 rats was injected with inoculum that had been heated to boiling in a waterbath for ten minutes. The groups receiving this inoculum served as controls for possible nonspecific reactions due to either altered protein or to dead acid-fast bacilli and their products. All animals were maintained on a diet of Purina Fox Chow.

Therapy with Promin[4], Diasone[5], Penicillin[6], and Streptomycin[7], was carried out as follows. Approximately 50 mg. of Promin were fed daily in the diet for the duration of the experiment. It was prepared by adding 4 mg. of Promin to each Gm. of food, of which each rat consumed from 10 to 15 Gm. per day. One-half Gm. of Diasone per Kg. of body weight was injected subcutaneously daily for five months beginning the day of inoculation. The Diasone was dissolved in an 0.85 per cent saline solution. A single dose of 1,000 units of aqueous sodium penicillin was injected subcutaneously near the point of inoculation daily for five months. In the case of streptomycin, three treatment schedules were evaluated; 25,000, 50,000, and 100,000 γ per Kg. of body weight daily. The streptomycin was injected at intervals of eight hours for five days, totaling 125,000, 250,000, and 500,000 γ per Kg. of body weight.

The therapeutic efficacy of streptomycin was evaluated only in advanced murine leprosy; namely, an infection which had progressed six months and exhibited well-developed lepromata, and in some instances ulcers, at the site of inoculation. In this experiment, both the "Harvard" and the "Puerto Rican" strains were injected into the left gastrocnemius muscle of one group of rats and subcutaneously near the sacral region of another. The latter area was selected to determine if lepromata on the back were less prone to secondary infection than ventrally located lesions. A third group was inoculated intramuscularly as described above with the "Puerto Rican" strain. Six months after inoculation all of the rats in the above groups had well-developed lepromata, and clinically the two strains were indistinguishable at the time therapy was initiated.

The animals were examined three times weekly for clinical evidence of disease. Lepromatous lesions, if present, were measured by the same person with the aid of a plastic ruler. Autopsies were performed on all animals at the time of death or whenever an experiment was terminated. Films for acid-fast bacilli were prepared routinely from tissue at the site of inoculation, from the liver, spleen, and lung, as well as from any other tissue where macroscopic abnormalities were observed. Cultures for evidence of intercurrent infection were made from the heart's blood and occasionally from other sites, provided that the condition of the animal was suitable for bacteriologic examination when examined post mortem. Whenever doubt existed concerning any lesion observed grossly, histologic sections were prepared and examined microscopically.

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[4] Promin was supplied by Parke-Davis and Company, Detroit, Michigan.

[5] Diasone was furnished by the Abbott Laboratories, North Chicago, Illinois.

[6] Penicillin was provided by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

[7] Streptomycin was made available by Merck and Company, Inc., Rahway, New Jersey; and by Squibb Institute for Medical Research, New Brunswick, New Jersey.

The course of the disease generally progressed in the following manner. After inoculation, the infected animal continued to gain weight and otherwise appeared normal for two to three months, at which time a palpable leproma usually formed at the site of inoculation. As the local lesion became larger, the infection spread to other organs, particularly to the adjacent lymph nodes, the spleen, liver, and lungs. The hair became coarse, alopecia developed, and the animal became emaciated. Subsequently, extensive ulcerations occurred over the lepromatous masses. Not infrequently epicardial lesions developed. Death usually occurred within eight to fourteen months after inoculation. During the advanced stages of the disease the animals were prone to intercurrent infection and care was taken to isolate such animals immediately.

RESULTS

Promin

A dosage of approximately 50 mg. of Promin administered daily as a component of the diet did not prevent the development of murine leprosy nor change the character of lesions typical of the disease. This dosage retarded the growth of the leproma at the site of inoculation, however, and delayed the progress of the disease, thereby increasing the survival time of treated rats. As soon as the infection became well established the pathogenesis of the experimental disease was not unlike that observed in untreated rats. Of 20 infected rats treated with Promin, one died of an intercurrent infection one week after the study was undertaken. A year later, 18 (95 per cent) of the remaining 19 rats still survived as compared with 15 (75 per cent) of a group of 20 untreated animals employed as controls. The physical condition of the treated rats was superior to that of the untreated controls, many of whom were moribund. Eighteen months after the experiment was undertaken only 2 (10 per cent) of the controls were living as compared with 9 (47 per cent) of the rats receiving Promin. In both groups of rats the disease was advanced, however, and because of their moribund state the animals were sacrificed (table 1).

Diasone

A dosage of 0.5 Gm. of Diasone per Kg. of body weight injected subcutaneously daily for five months failed to suppress the development of lepromata. The course of the disease in the treated rats progressed like that of the untreated controls and 14 (93 per cent) of 15 treated rats had nodules from 0.5 cm. to 2.0 cm. in diameter at the time the drug was withdrawn. One of the rats had died as a result of an accident. Seven (70 per cent) of 10 untreated controls had similar lesions. Ten months after inoculation, 12 (80 per cent) of the rats receiving Diasone still survived. They were very ill, however, and 6 had large lepromatous ulcers at the site of inoculation. Seven (70 per cent) of the untreated rats were living, 2 of which had ulcerating nodules comparable to those present in the treated group. During the next month so many deaths occurred as a result of an intercurrent pulmonary infection the experiment was terminated (table 1).

Penicillin

Therapy with a single daily dose of 1,000 units of aqueous sodium penicillin for five months failed to influence the course of the disease and the treatment was discontinued. Seventeen (85 per cent) of 20 animals had lepromata from 0.5 cm. to 2.0 cm. in diameter. Fifteen (75 per cent) of 20 untreated controls had similar nodules. The experiment was terminated one year after treatment was initiated, at which time 12 (86 per cent) of 14 of the surviving rats had large lepromatous ulcers as compared with only 6 (40 per cent) of 15 untreated controls. As a matter of fact, the general physical condition of the surviving treated

TABLE 1

Comparative Therapeutic Efficacy of Promin, Diasone, and Penicillin in Experimental Murine Leprosy

DRUG	GROUP	NUMBER RATS	MONTHS AFTER INOCULATION	SURVIVALS	
				Number	Per cent
Promin	Treated*	19†	5	19	100
			12	18	95
			18	9	47
	Controls	20	5	20	100
			12	15	75
			18	2	10
Diasone	Treated‡	15	5	14	93
			10	12	80
	Controls	10	5	9	90
			10	7	70
	Heated inoculum	5	5	5	100
			10	5	100
Penicillin	Treated§	20	5	20	100
			12	14	70
	Controls	20	5	20	100
			12	15	75

* Approximately 50 mg. administered in the diet daily for duration of experiment.

† 20 animals in original group; one died of an intercurrent infection one week after inoculation.

‡ Administered 0.5 Gm. per Kg. body weight daily, subcutaneously for 5 months.

§ Administered 1,000 units daily, subcutaneously for 5 months.

rats was considerably worse than that of the untreated controls, all of whom showed marked evidence of disease (table 1).

Streptomycin

Streptomycin in the dosages employed did not retard the progress of advanced lesions of murine leprosy. The survival time of some of the treated animals exceeded that of the untreated rats by one to two months. The average survival time of 15 rats treated with a total dosage of 125,000 γ per Kg. of body weight was 9.7 months, of 15 treated with 250,000 γ per Kg. of body weight was 10.4 months, and of 18 treated with 500,000 γ per Kg. of body weight was 9.1 months.

The average survival time of 15 untreated controls was 9.0 months. The rats receiving 50,000 γ of streptomycin per Kg. of body weight per day survived on the average of 1.4 months longer than the controls. The rats treated daily for five days with 25,000 and 100,000 γ of streptomycin per Kg. of body weight showed little increase in longevity over the untreated control animals (table 2). No difference in the resistance of the two strains of murine leprosy to streptomycin was detected.

The group of 20 control rats injected with the heated inoculum remained normal throughout the 18 months' observation period, at which time they were sacrificed. Films prepared from tissue removed from the site of inoculation showed no acid-fast bacilli.

TABLE 2

Evaluation of Streptomycin in Advanced Murine Leprosy

DAILY DOSAGE	TOTAL DOSAGE 5 DAYS	NUMBER RATS	AVERAGE MONTHS SURVIVAL
γ per Kg. body weight			
25,000	125,000	15	9.7
50,000	250,000	15	10.4
100,000	500,000	18	9.1
Untreated	Controls	15	9.0
Heated inoculum	Controls	15	18.0*

* Sacrificed after 18 months.

DISCUSSION

Evaluation of the therapeutic efficacy of drugs in leprosy is difficult because observation of the patient is required from the time therapy is initiated until death occurs. In murine leprosy the problem is still laborious because approximately one year is required to complete a single experiment. Nevertheless, data that may be valuable in solving the problems of Hansen's disease can be accumulated comparatively rapidly from studies of the experimental infection in rats. It is significant that the results obtained with Promin, Diasone, penicillin, and streptomycin in murine leprosy are not inconsistent with the information acquired to date on the treatment of leprosy in man. None of the four agents effected a cure, but Promin markedly suppressed the infection in rats. Furthermore, the general health of this group of animals during the course of the disease was superior to that of the untreated controls. In these preliminary studies, only a single dose of the drug was tested, except in the case of streptomycin. Although the amounts of the drugs employed were in the same range as those used in man, as yet only the effect of the minimal dosage has been observed. Furthermore, in our studies Promin was administered orally with the food, whereas it was injected intravenously for the treatment of human leprosy (8). Unfortunately, facilities and personnel were not available to test a series of dosage levels.

In animals with advanced lesions, streptomycin appeared to possess only minimal therapeutic value, even with dosages equivalent to 6,000,000 γ per day for a man weighing 60 Kg. It was anticipated, however, that treatment for a five day period would probably be inadequate. More recent studies, which will be reported later, on the therapeutic efficacy of streptomycin in early murine leprosy, in which the treatment was initiated on the day of inoculation and carried out for several weeks, are likewise disappointing. These observations are in contrast to preliminary studies *in vitro* on the effect of streptomycin on *Mycobacterium leprae murium* in suspensions of lepromatous tissue. In these experiments

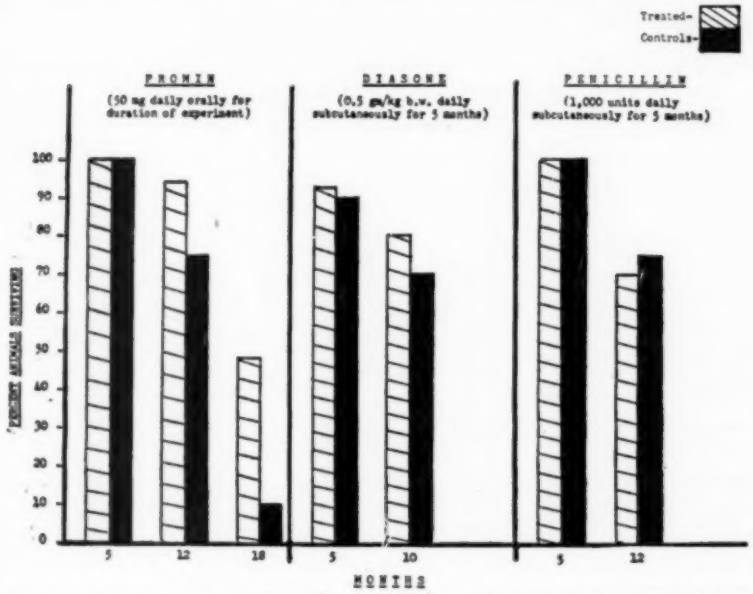

FIG. 1. Comparative therapeutic efficacy of Promin, Diasone, and penicillin in experimental murine leprosy.

the drug appeared to exert rather marked bacteriostatic and bactericidal action as determined by animal inoculation of the treated suspensions.

Therapy for five months with either Diasone or penicillin failed to alter significantly the course of the disease. Although treatment was not continued throughout the course of the disease, as was the case with Promin, it was obvious at the termination of therapy that no benefit was being dervied from their use.

The above observations constitute only modest beginnings in this field and do not engender pessimism. Because of the slowly progressive character of murine leprosy, many months were required to become thoroughly familiar with the infection in order to develop a uniform experimental disease. With a rat colony now well established, much more rapid progress can be made.

SUMMARY

1. The therapeutic efficacy of Promin, Diasone, and penicillin in early murine leprosy has been compared, employing dosages approximating those used in the treatment of leprosy in man. Streptomycin was evaluated in advanced murine leprosy only.

2. Approximately 50 mg. of Promin, administered daily with the diet, suppressed the infection in rats and increased their longevity compared to that of untreated controls, but failed to effect a cure.

3. Streptomycin, employing daily dosages of 25,000, 50,000, and 100,000 γ per Kg. of body weight, administered subcutaneously every eight hours for five days, had minimal therapeutic effects on advanced murine leprosy.

4. Neither Diasone, 0.5 Gm. per Kg. of body weight, nor aqueous sodium penicillin, 1,000 units injected subcutaneously daily for five months, altered significantly the course of the disease.

SUMARIO

Quimioterapia de la Lepra Murina

1. Empleando dosis aproximadas a las usadas en el tratamiento de la lepra en el hombre, comparóse la eficacia terapéutica de la promina, la diasona y la penicilina en la lepra murina temprana. La estreptomicina fué valorada solamente en la lepra murina avanzada.

2. Aproximadamente 50 mg. de promina administrados a diario con el alimento suprimieron la infección en las ratas y acrecentaron su longevidad, comparada con la de los testigos no tratados, pero no efectuaron la curación.

3. La estreptomicina, empleada a dosis diarias de 25,000, 50,000 y 100,000 γ por kg. de peso y administrada subcutáneamente cada ocho horas durante cinco días, ejerció minimo efecto terapéutico sobre la lepra murina avanzada.

4. Ni la diasona, 0.5 gm. por kg. de peso del animal, ni la penicilina sódica acuosa, 1,000 unidades, inyectadas subcutáneamente a diario durante cinco meses, alteraron en forma significativa la evolución del mal.

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THE EVALUATION OF ANTITUBERCULOUS AGENTS WITH AVIAN TUBERCULOSIS IN CHICKS: A COMPARISON OF DIHYDROSTREPTOMYCIN AND STREPTOMYCIN[1]

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INTRODUCTION

The successful use of streptomycin as a therapeutic agent for certain forms of tuberculosis has resulted in efforts to develop additional and improved antituberculous agents and improved methods for *in vitro* and *in vivo* evaluation of such agents (1, 2). The guinea pig and the rabbit are highly susceptible to human and bovine types of *M. tuberculosis*, and consequently were the first animals used for studies on the efficacy of antituberculous agents. However, tests using these animals require 60 days for evaluation if acute infections are used, and 120 days if chronic infections are induced. A more rapid and economical test using mice and requiring only 28 days for completion has been introduced by Youmans (3,4). Martin (5) also recommends the mouse test.

Although it has been known that avian tuberculosis can be produced experimentally in the natural host (6), to our knowledge this infection has not hitherto been investigated as a method for the evaluation of antituberculous agents. Studies in this laboratory showed that a rapid and satisfactory infection could be produced in chicks by intravenous inoculation of avian type tubercle bacilli and that the infection responded to treatment with streptomycin. Furthermore, good correlation was observed between the level of drug dosage and response to treatment. The availability of dihydrostreptomycin offered an opportunity to apply the chick test to a comparative evaluation of streptomycin and dihydrostreptomycin.

Dihydrostreptomycin was first described by Peck, *et al.* (7) and shortly thereafter Youmans, quoted by Bartz, *et al.* (8), found that its *in vitro* antituberculous activity was the same as that of streptomycin. Freedlander and French (9) then reported that both drugs had equal *in vivo* activity against experimental tuberculosis in guinea pigs. On the other hand, Donovick and Rake (10) reported that dihydrostreptomycin showed significantly lower *in vitro* antituberculous activity than streptomycin; in a more recent publication (14), however, they report the two drugs to be equal in activity. One of us, in a recent report by Edison, *et al.* (11), summarized the results of a comparison of the efficacy of dihydrostreptomycin and streptomycin against avian tuberculosis, stating that these drugs were similar in antituberculous activity both by *in vitro* and *in vivo* tests. The present report is concerned with a description of the chick efficacy test and its application to the evaluation of streptomycin and dihydrostreptomycin.

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MATERIALS AND METHODS

M. tuberculosis, human type, strain H37Rv and avian type, strain Kirchberg, were used in these studies. The strains have been maintained by weekly serial passage in Dubos Tween-albumin medium. The drugs used were streptomycin calcium chloride complex (crystalline), 87.5 per cent pure[3] and dihydrostreptomycin trihydrochloride (crystalline), 95 per cent pure[3].

Technique for in vitro Tests

Tests were performed both with Dubos Tween-albumin medium (2) and with Youmans' modification of Proskauer and Beck's synthetic medium (1). One ml. amounts of aqueous drug solution sterilized by Seitz filtration were added to 9 ml. amounts of medium. The tubes were then inoculated with 0.1 ml. amounts of a 1:10 dilution of culture in Dubos medium adjusted with a Coleman 6A spectrophotometer to permit 90 per cent transmission of light at 620 mu. The test cultures were observed for the presence of growth after 14 days of incubation at 37°C.

Technique for in vivo Tests

One-to-three weeks old male white leghorn chicks were used. The animals were fed a diet of Startena[4] ad libitum and were housed in an air-conditioned room at a temperature of 80°F. In each experiment, the chicks were divided into groups of 10 having comparable average weights. The animals were infected intravenously with 0.5 ml. amounts of 14 to 21 day old culture in Dubos medium adjusted with a Coleman 6A spectrophotometer to permit 60 to 63 per cent transmission of light at 620 mu.

Treatment was by the intramuscular route and was given six days per week for a period of six or seven weeks. The drug solutions were prepared with distilled water to contain the desired daily dose per animal in 0.25 ml. of solution. The animals were weighed once weekly and the estimated weight gain for the next week was projected by analysis of the slope of the growth curve during the previous week. The drug dosage for the week was then calculated from the projected average weight. As subsequently determined from the observed weights, the error in dosage was rarely greater than 5 per cent; greater deviations occurred only when animals were in the terminal phase of infection.

The chicks surviving at the end of the test period as well as those dying during the course of the experiment were autopsied. The total body weights and the weights of the liver and the spleen were recorded. Pieces of liver, spleen, kidney, and lung were fixed in 10 per cent formalin. Histologic sections were stained with hematoxylin and eosin and, in the case of the liver, with an acid-fast stain.

To determine the extent and degree of the histopathologic changes, the following factors were analyzed:

I. *The number of tubercles per low power field:* 1 plus, indicating less than ten; 2 plus, ten to thirty; 3 plus, thirty to fifty; and 4 plus, over fifty.

II. *Amount of tissue replaced or displaced by the tubercles as observed per low power field:* 1 plus, equivalent to less than 10 per cent; 2 plus, 10 per cent to 33 per cent; 3 plus, 33 per cent to 50 per cent; and 4 plus, over 50 per cent.

III. *The developmental stage of the tubercles:* Preliminary studies confirmed Feldman's description of the pathogenesis of the miliary tubercle (7). The different stages in the development of the tubercle were arbitrarily divided. Not all the lesions in any one organ were at the same stage but they were sufficiently uniform to fall into one of the following stages:

1. Small collections of epithelioid cells are observed.

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[3] Purity estimated by rotation. These figures were obtained from Dr. T. J. Webb of The Research Laboratories of Merck & Co., Inc.

[4] Produced by Ralston-Purina Company, St. Louis, Missouri.

2. Tubercles are larger and composed of epithelioid cells and a thin rim of histiocytes, lymphocytes, and an occasional granulocyte.
3. The epithelioid cells are fused and vacuolated.
4. Necrotic changes are present within the tubercle.
5. The centers of the tubercles are composed of necrotic epithelioid cells bordered by a layer of epithelioid syncytia and giant cells. The outer zone is composed of epithelioid cells, histiocytes, and a few fibroblasts and lymphocytes. Amyloid-like deposits may be present.
6. At this stage the mature tubercle is found. It is composed of four zones: an inner necrotic zone; a zone of giant cells; a zone of epithelioid cells and histiocytes; and finally a zone of histiocytes, fibrous tissue elements, lymphocytes, and amyloid-like deposits.

IV. *Cellular reaction:* The degree of cellular reaction was estimated by the number of layers that the lymphocytes and granulocytes formed about the average-sized tubercle seen in the section. One cell layer was indicated by 1 plus, two cell layers by 2 plus, three cell layers by 3 plus, and four or more cell layers by 4 plus.

TABLE 1

Effect of Various Doses of Streptomycin on Mortality of Chicks Infected with M. tuberculosis Avian Type, Strain Kirchberg

GROUP NUMBER	DOSE UNITS PER KG. PER DAY	TREATMENT STARTED, WEEKS AFTER INJECTION	MORTALITY PER CENT
1	50,000	0	0
2	10,000	0	20
3	2,000	0	70
4	50,000	2	20
5	10,000	2	90
6	2,000	2	90
7	—	—	80
8	50,000	Not infected	0
9	10,000	Not infected	0
10	2,000	Not infected	0
11	—	Not infected	0

PROCEDURE AND RESULTS

The results of the *in vitro* tests showed that both drugs inhibited avian type, strain Kirchberg at a concentration of 5 γ per ml. and human type strain H37Rv at a concentration of 0.5 γ per ml. The results were the same in Youmans' modification of Proskauer-Beck medium and in Dubos Tween-albumin medium.

The effect of graded doses of streptomycin was studied in experiment 1. The chicks were divided into groups treated as shown in table 1 and the experiment was terminated 50 days after infection.

The data on survival, presented in table 1, indicated that streptomycin was effective and that efficacy was directly correlated with level of drug dosage. Twenty per cent of the infected controls were alive at the end of the experiment. Among the groups treated immediately after infection, 100 per cent of the 50,000 unit group, 80 per cent of the 10,000 unit group, and 30 per cent of the 2,000 unit group were still alive. When treatment was delayed for 2 weeks, the survival rates

were respectively 80 per cent, 10 per cent, and 10 per cent for the 50,000, 10,000 and 2,000 unit groups.

Inspection of growth curves, shown in figure 1, indicates that animals receiving 50,000 units per day beginning immediately after infection, as well as the uninfected controls treated with streptomycin, gained weight at the same rate as normal controls. With treatment at the 10,000 unit level begun immediately after infection and at the 50,000 unit level begun two weeks after infection (not included in figure 1), the rate of growth was depressed. Chicks in the

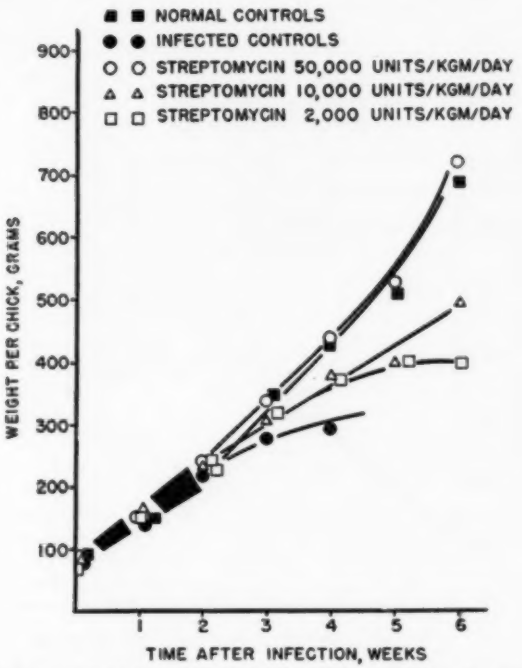

FIG. 1. Growth curves of chicks infected with avian tuberculosis and treated with various doses of streptomycin.

2,000 unit groups and in the 10,000 unit group given delayed treatment (not shown in figure 1) gained weight at a decreasing rate and at the sixth week their weights tended to remain stationary or to decline. The growth curves of the animals in these groups were above those of the infected controls.

The efficacy of dihydrostreptomycin as compared with streptomycin was studied in experiments 2 and 3. In experiment 2 the drugs were administered on an equal weight basis which did not compensate for differences in the estimated purity. The higher dose was established at 77 mg. per Kg. per day; this dose was equivalent to 50,000 units per Kg. per day. In experiment 3 the drug dosage was

adjusted to compensate for the differences in estimated purity. The higher dose of streptomycin was again 77 mg. per Kg. per day and dihydrostreptomycin now 65.5 mg. per Kg. per day. The lower doses were again one-tenth those of the higher ones.

The comparative efficacy of the antituberculous agents in these experiments was evaluated by an analysis of growth curves, mortality data, and pathological changes in the liver. The growth curves for experiment 2 are shown in figure 2, those for experiment 3 were similar and are therefore not presented graphically.

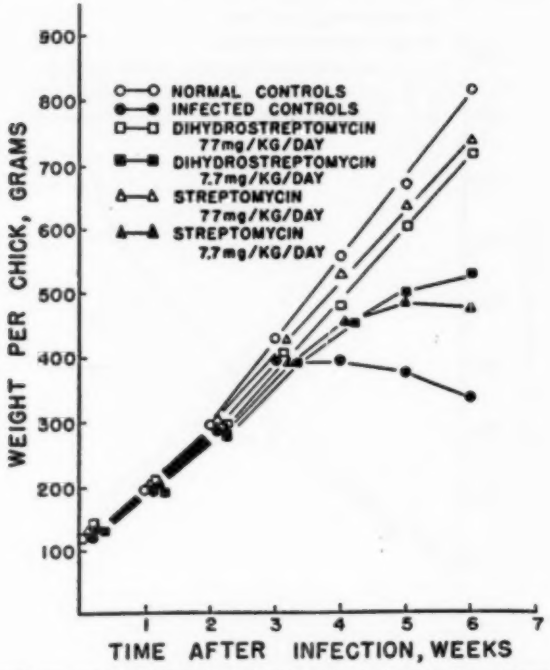

FIG. 2. Growth curves of chicks infected with avian tuberculosis and treated with streptomycin or dihydrostreptomycin.

The mortality data and data on the amount of liver tissue replaced by tubercles are given in table 2. The pathological findings for experiment 3 are further summarized in table 3.

In both comparative tests the infected control animals gained weight at a normal rate for the first 2 weeks and then showed a progressively decreasing rate of growth. Deaths occurred beginning with the third week. At the end of the sixth week 80 per cent of the controls were dead in experiment 2 and 90 per cent in experiment 3. Animals treated with the higher level of both drugs in both experi-

ments gained weight at a rate slightly below that of normal chicks and the drug control groups. There were no significant differences between the weight curves of the groups given the higher doses of either drug.

At the lower dosage level, differences were observed in the rate of mortality which could be correlated with the amount of drug administered. In experiment 2, where identical weights of drug were used, no deaths were observed among chicks treated with dihydrostreptomycin but 50 per cent of the chicks treated

TABLE 2

Effect of Streptomycin and Dihydrostreptomycin on Mortality and Tissue Involvement of Chicks Infected with M. tuberculosis Avian Type, Strain Kirchberg

GROUP	DRUG	DOSE MG. PER KG.		MORTALITY PER CENT	AMOUNT OF LIVER TISSUE REPLACED BY TUBERCLES. AVERAGE OF GROUP
			Experiment 2		
1	Streptomycin	77.0	Not infected	0	—
2	Streptomycin	77.0	Infected	0	1.7+
3	Streptomycin	7.7	Infected	50	3.1+
4	Dihydrostreptomycin	77.0	Not infected	0	—
5	Dihydrostreptomycin	77.0	Infected	0	1.5+
6	Dihydrostreptomycin	7.7	Infected	0	3.0+
7	None	—	Infected	80	4.0+
8	None	—	Not infected	0	—
			Experiment 3		
1	Streptomycin	77.0	Not infected	0	—
2	Streptomycin	77.0	Infected	0	1.7+
3	Streptomycin	7.7	Infected	50	3.8+
4	Dihydrostreptomycin	65.5	Not infected	0	—
5	Dihydrostreptomycin	65.5	Infected	0	1.9+
6	Dihydrostreptomycin	6.6	Infected	40	3.1+
7	None	—	Infected	90	3.8+
8	None	—	Not infected	0	—

with streptomycin were dead at the end of the sixth week. In experiment 3, in which the amount of dihydrostreptomycin administered was lowered to compensate for the higher purity as compared with streptomycin, the mortality at the end of the sixth week for the dihydrostreptomycin treated group was 40 per cent as compared with 50 per cent for the group treated with streptomycin.

The growth curves for animals receiving the lower dose of drug were intermediate between those for groups receiving the higher dose of drug and the infected control group. The rate of growth at the lower drug dosage began to decline in the third week and decreased progressively thereafter. In experiment 2

the growth curves were closely similar until death ensued in the streptomycin-treated group, whereas in experiment 3 the dihydrostreptomycin-treated chicks gained weight more rapidly than those treated with streptomycin.

TABLE 3

Histopathological Changes in Livers of Treated and Untreated Chicks Infected with Avian Tuberculosis, Strain Kirchberg

Experiment 3

GROUP NUMBER	CHICK NUMBER	NUMBER OF TUBERCLES	AMOUNT OF TISSUE INVOLVED	AGE OF TUBERCLES	DEGREE OF CELLULAR REACTION	DIED OR SACRIFICED
I. Infected not treated	228	4+	4+	4	0+	D
	229	1+	2+	3	4+	S
	230	4+	4+	4	0+	D
	231	4+	4+	4	0+	D
	232	4+	4+	4	0+	D
	233	4+	4+	3	1+	D
	234	4+	4+	4	1+	D
	235	4+	4+	4	0+	D
	236	4+	4+	4	0+	D
	237	4+	4+	4	0+	D
II. Infected treated with streptomycin 77 mg. per Kg.	238	3+	2+	1	2+	S
	239	3+	2+	2	2+	S
	240	3+	2+	1	3+	S
	241	2+	2+	2	2+	S
	242	3+	2+	2	2+	S
	243	2+	1+	2	3+	S
	244	3+	2+	1	2+	S
	245	3+	2+	2	4+	S
	246	1+	1+	1	4+	S
	247	1+	1+	2	4+	S
IV. Infected treated with dihydrostreptomycin 65.5 mg. per Kg.	258	2+	1+	1	3+	S
	259	3+	3+	3	3+	S
	260	2+	2+	1	1+	S
	261	2+	1+	2	3+	S
	262	1+	2+	1	4+	S
	263	2+	2+	1	2+	S
	264	3+	2+	2	2+	S
	265	2+	2+	1	2+	S
	266	2+	2+	1	4+	S
	267	2+	2+	1	4+	S

The histopathologic findings in both experiments were similar (table 3). The livers of the infected controls, most of which died before the test was terminated at 42 days, showed that more than 75 per cent of the tissue field was replaced by tubercles (4 plus lesion), the maximum amount of tissue reaction that could be expected at this stage of the disease. Little or no lymphocytic reaction was seen about the tubercles. The spleens revealed a similar histopathologic picture and

the weights of both livers and spleens of the infected controls were greater than in the drug-control or normal control birds. The lungs and kidneys presented only an occasional tubercle.

Both streptomycin and dihydrostreptomycin had a definite effect on the histopathologic picture. At the higher level of treatment with both drugs, the tubercles in the livers involved or displaced less tissue, were fewer, smaller, at an earlier stage, and were surrounded by a distinct coat of infiltrated cells, principally lymphocytes. The effect on the spleens paralleled that seen in the livers but was more variable. The weights of the livers and spleens of these treated animals averaged the same as normal uninfected birds, namely 5 per cent and 0.5 per cent, respectively, of the total body weight as compared with 15 per cent and 0.8 per cent of the total body weight in the infected controls. The increase in

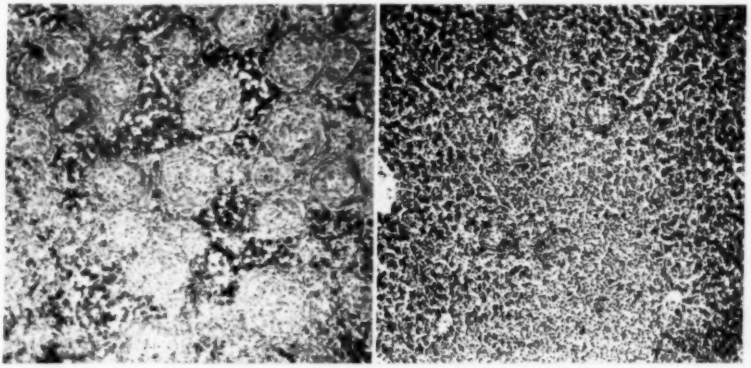

FIG. 3A. (Left) Liver of infected control chick, 6 weeks after infection.

FIG. 3B. (Right) Liver of infected chick treated with 65.5 mg. of dihydrostreptomycin per Kg. per day, 6 weeks after infection.

weights of the livers and spleens in infected birds, both treated and untreated, corresponded with the amount of tuberculous involvement.

In birds receiving one-tenth of the higher dose, the effect of both drugs was still quite noticeable. It will be recalled that at these levels the growth curves were above those for the infected controls, and a higher proportion of the treated animals as compared with infected controls were alive at the end of the test period. Microscopic examination of the livers, however, showed a degree of tuberculous involvement approaching that seen among infected controls. The extent of involvement in the spleen was less than that observed in the controls, but there was considerable variation in the reaction among individual treated animals.

Sections of liver stained by an acid-fast technique revealed that the number of acid-fast bacilli present in the tubercles was directly correlated with the degree of tuberculous involvement.

Photomicrographs of liver from an infected control chick and a treated chick

are shown in figure 3. Four small lesions may be seen in the section of the liver of the treated animal.

In addition to the three trials used in the present studies, seven other chick tests have been performed with the same infecting inoculum. In all but one of the 10 trials, 80 to 100 per cent of the infected controls were dead by the end of the seventh week. The rate of growth for chicks in all trials began to decline between the third and fourth weeks and decreased rapidly thereafter.

DISCUSSION

Avian tuberculosis is now used by our laboratory as one of the *in vivo* screening methods for antituberculous activity. This infection shows a number of desirable features. The test animal is a natural host for the disease, the host-parasite relationship shows a low degree of variability, and the relationship can be controlled readily. In addition, the chick is a desirable experimental animal because its genetic lines and nutritional requirements are well known and significant intercurrent infections are minimal at this age. There is also a low risk of laboratory infection because avian type rarely produces disease in man.

With the chick test, highly reproducible assessment of comparative efficacy may be expected. The results show that the factors studied to determine the degree of tuberculous involvement, namely, mortality rates, growth curves, microscopic changes, weights of liver and spleen, and the number of acid-fast bacilli present in the liver, were generally directly correlated with each other. We have observed a higher degree of variability for mortality rates and appearance of tuberculous lesions in mice infected with human type. As has been emphasized by other investigators, however, mortality by itself is not a highly reliable index of efficacy. The inhibition or regression of tuberculous lesions is the more reliable criterion.

In this regard, observations of both gross and microscopic changes may be used in assessing efficacy by mouse and guinea pig test methods. In the chick, the acute infection used in this study does not lead to the formation of gross lesions. Consequently, the pathological alterations in the tissues are determined by microscopic examination. The uniformity of the distribution of the lesions and their characteristic appearance simplify the evaluation of the pathological changes.

The growth curve in the chick test is a useful index of morbidity because the progressive decrease in the rate of growth of infected chicks as compared with the normal controls closely parallels the development of the tuberculous lesions. The rate of growth is also useful in the guinea pig test, but the growth of guinea pigs does not follow as precise and predictable a trend as is observed with chicks. In the mouse test, a significant decline in animal weight occurs only in the terminal phase of infection.

The chick test, however, does not completely replace *in vivo* tests with human type in guinea pigs or mice, since the agents to be tested may not possess the same degree of activity against both human and avian type. This difference, as

determined by *in vitro* tests, should indicate the degree of reliance that may be placed upon the chick, test.

Our *in vitro* studies, showing that *M. tuberculosis* human type is equally sensitive to streptomycin and dihydrostreptomycin, are in agreement with the findings of Youmans and Karlson (12) and Feldman, *et al.* (13). Similarly the avian type is equally sensitive to both drugs. However, avian type is more resistant than human type to the action of both drugs.

Although the avian type was more resistant than human type to the action of streptomycin and dihydrostreptomycin *in vitro* and the test chicks were given a massive infecting inoculum, the infection was relatively sensitive to the action of both drugs. Reports by other investigators indicate that, with mice, doses of streptomycin in the range of 20,000 to 100,000 units per kg. per day and, with guinea pigs, 15,000 units per Kg. per day are adequate to produce a good therapeutic response. In the chick a dose of 10,000 units per Kg. per day produced a detectable therapeutic effect and 50,000 units were required to produce a marked effect. The chick thus compares favorably with the guinea pig or mouse when considering sensitivity of response to streptomycin or dihydrostreptomycin. The dosage range of 10,000 to 50,000 units per Kg. per day corresponds roughly to a range of 0.5 to 3 Gm. per day for man.

Our *in vivo* studies showing that dihydrostreptomycin is as active as streptomycin are in agreement with the findings of Freedlander and French (9) and Feldman, Karlson and Hinshaw (13) using human type in the guinea pig, and Rake, *et al.* (14) using bovine type in the mouse.

The data in this report do not indicate the effect of treatment on a well-established tuberculous process.

SUMMARY

1. A new *in vivo* test for assessment of antituberculous activity is described which employs intravenous inoculation of chicks with avian type of *M. tuberculosis*. This test gives highly reproducible results. The effect of treatment is evaluated on the basis of growth curves, mortality data, and histopathologic changes in the liver. The last includes the number of tubercles, the amount of tissue displaced or replaced by the tubercles, the age of the tubercles, and the degree of lymphocytic and granulocytic reaction.

2. The method is applicable to substances showing comparable *in vitro* activity against human and avian types.

3. This test, applied to a comparison of the efficacy of dihydrostreptomycin and streptomycin, indicates that these drugs are of comparable efficacy against avian tuberculosis in the chick.

SUMARIO

Valuación de los Agentes Antituberculosos con la Tuberculosis Aviaria de los Pollos: Comparación de la Dihidroestreptomicina y la Estreptomicina

1. El nuevo ensayo *in vivo* aquí descrito para la valoración de la actividad antituberculosa utiliza la inoculación intravenosa de los pollos con el tipo aviario

del *M. tuberculosis*. Este ensayo da resultados muy reproducibles. El efecto del tratamiento se valúa a base de las curvas del desarrollo, los datos de mortalidad y las alteraciones histopatológicas en el hígado, comprendiendo estas últimas: número de tubérculos, proporción de tejido desplazado o suplantado por los tubérculos, edad de los tubérculos e intensidad de la reacción linfocitaria y granulocitaria.

2. El método tiene aplicación a sustancias que revelen actividad *in vitro* comparable contra los tipos humano y aviario.

3. Este ensayo, aplicado a una comparación de la eficacia de la dihidroestreptomicina y la estreptomicina, indica que estas drogas poseen eficacia comparable contra la tuberculosis aviaria en el pollo.

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ROUTINE CHEST PHOTO-ROENTGENOGRAPHY IN BARONESS ERLANGER HOSPITAL, CHATTANOOGA, TENNESSEE

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INTRODUCTION

Since 1930, there have been occasional references in the literature to articles evaluating routine chest roentgenography of individuals admitted to general hospitals. Perhaps the most outstanding of these articles was that of Plunkett and Mikol in 1940 (1). These writers reviewed preceding articles by others and, in addition, reported the results of a study of routine chest roentgenograms in nearly five thousand persons admitted to fourteen general hospitals. They stated:

> Because of the existence of tuberculosis in some of the patients who are admitted to general hospitals for other conditions, they constitute a population group of considerable importance in the epidemiology of tuberculosis. While to the individual patient early diagnosis is important, the significance of this to the hospital personnel, the family and the community deserves emphasis. Although x-ray films will discover these cases, nevertheless, the x-ray has not been as commonly used as the need would indicate for the diagnosis of not only tuberculosis but also other diseases of the chest.

The State Department of Public Health, acknowledging such a need in Tennessee, offered to Baroness Erlanger Hospital in Chattanooga the permanent loan of 70 mm. photo-roentgen equipment for the purpose of doing chest roentgenograms routinely on all persons admitted to the hospital. This offer was accepted early in 1946 and the unit was delivered in March of the following year. Previously there had been put into use by the Chattanooga-Hamilton County Health Department a stationary photo-fluorograph for clinic use, and a mobile unit for mass roentgenographic examination of persons in industry, schools, and communities. The equipment was placed at the general hospital, therefore, to round out the case-finding program and to make available to another population group routine chest roentgenograms for the discovery of cases of tuberculosis.

A brief comparison of the amount of tuberculosis found by the three photo-roentgen survey units now operating in Chattanooga is the purpose of this paper.

METHOD OF PROCEDURE

The stationary 35 mm. photo-fluorograph in the Health Department clinic has been used since June 1944 to examine foodhandlers, contacts, teachers, barbers, and beauty operators, persons applying for employment in certain industries (pre-employment), patients referred by physicians, persons desiring roentgenograms because of symptoms or for some other reason, a few students referred from schools, and a miscellaneous group designated as "other." Hereafter, the individuals included in this survey will be described as the "Clinic Group".

The mobile unit, a 70 mm. photo-fluorograph installed therein, has been in use since

[1] Chattanooga-Hamilton County Health Department.

March 1946. The population groups surveyed by this unit have been classified as community, industrial, and school. The classifications are for the most part self-explanatory. The community group includes persons in the various sections of Chattanooga and Hamilton County who are adults living in residential areas. The industrial group in Hamilton County consists primarily of workers employed in textile plants, foundries, and metal factories, and in various small metal, wood, and machine shops or factories. The school group is made up of students 15 years of age or over. The term "mobile unit" will be used to refer to this whole group.

In Baroness Erlanger Hospital it was planned to obtain chest roentgenograms routinely on all persons admitted to the hospital, but this was not attempted during the first year. Included in the survey group are employees and service patients (any nonpaying patients, primarily indigent), and also a few private patients and persons referred from the emergency room. The term "hospital group" will be used in referring to this group of persons.

Analyses of the results of all three surveys were not made during the same year but the results are, nevertheless, readily comparable. Analyses of the clinic and mobile unit groups are for the year 1946, and analysis of the hospital group is for the period April 1 through December 31, 1947. An early report of this sort seems indicated because of the relatively high percentage of pulmonary tuberculosis discovered during the first year in the group of persons who were routinely examined roentgenographically on admission to the hospital.

TABLE 1

Results of Photo-roentgen Examinations from Three Types of Surveys
Chattanooga-Hamilton County
1946–1947

GROUP	NUMBER EXAMINED	CASES	
		NUMBER	PERCENT
Health department clinic, 1946	13,966	383	2.7
Mobile unit, 1946	14,293	290	2.0
Hospital unit, 1947	5,187	193	3.7
All surveys	33,446	866	2.6

SURVEY FINDINGS

Thus far approximately 113,500 examinations were made with the photofluorographic units in a community with a population of 193,591[2]. In 1946, as may be seen in table 1, there were 13,966 first examinations at the clinic, 14,293 first examinations at the mobile unit, and in 1947 there were 5,187 first examinations at the hospital. The number of cases of tuberculosis discovered as a result of first examinations in the combined surveys and in different types of surveys may be seen in table 1.

In the three types of surveys combined, 33,446 patients received chest roentgenograms for the first time. Of this group, 866 persons, or 2.6 per cent, were found to have definite tuberculosis (table 1). In contrast to this average rate for the whole group, the percentage of persons found to have tuberculosis on examination at the mobile unit was 2.0, while in the Health Department clinic the percentage was 2.7. In the hospital group the relatively high percentage of 3.7 persons with tuberculosis was discovered.

[2] Estimated population in 1946, Tennessee Department of Health.

The efficiency of the three types of surveys in finding cases of tuberculosis in the population may also be seen in table 1. Three and seven-tenths per cent of the hospital group were discovered to have tuberculosis in contrast to 2.7 of the Health Department clinic group and 2.0 of the mobile unit group.

DISCUSSION

Although the highest percentage of cases of tuberculosis (3.7) was found in the hospital group, the finding of 2.0 and 2.7 per cent of persons examined with tuberculosis in mobile unit and clinic groups should not be minimized. Such surveys have proved their value during recent years and there are many references in the literature concerning the success of mass roentgenographic studies. Nevertheless references to articles setting forth the value of routine roentgenographic examination of hospital admissions are rather few and far between. Such articles as are found stress the risk to the medical student, nurse, or hospital employee of cases of unrecognized tuberculosis in the hospital population, but few dwell at any length on the exceptional opportunity for tuberculosis case finding provided by the hospital population. Moreover, references to the responsibility of general hospitals in the case-finding program are strikingly absent from the literature. It would seem that the finding of a high percentage of cases of unrecognized tuberculosis among hospital employees and patients imposes a responsibility that is difficult to ignore.

It is of interest to consider briefly the makeup of the hospital survey group as compared to the Health Department clinic group. The mobile unit population composition is obvious from the titles of the previously mentioned subgroups (industry, community, school). In none of these subgroups has the finding of tuberculosis been higher than 2.7 per cent. There is no outpatient tuberculosis clinic in connection with Baroness Erlanger Hospital, and patients are admitted for hospital and clinic services for any of the many reasons for which general hospitals admit and care for patients. Outside of the fact that the patient enters the hospital or outpatient department for some complaint other than tuberculosis, and except for diabetic, tumor and veneral disease clinics (which might be expected to have considerable unrecognized tuberculosis), there is no special subgroup that contributes to the high percentage (3.7) of persons found in the hospital population with tuberculosis. On the other hand, in the clinic were examined such subgroups as contacts (5.5 per cent with tuberculosis), barbers and beauty operators (7.7 per cent), and patients referred by physicians (9.3 per cent), in all of whom cases of tuberculosis were discovered relatively frequently. This makes it all the more apparent that routine chest roentgenographic examinations of patients admitted to general hospitals should be seriously considered as a responsibility of the hospital and as its contribution to the community tuberculosis control program.

The success of any tuberculosis case-finding program depends upon the finding of early cases of the disease. In the clinic and mobile unit groups it was not unusual to find that 65 to 70 per cent of the lesions discovered were minimal in extent. For this reason it was quite surprising to learn that among the hospital

population examined 92 per cent of the lesions were minimal in extent. In only 7 per cent of the patients were the lesions moderately advanced and in only one per cent were the lesions far advanced. Minimal active lesions comprised 21 per cent of the total number of cases of tuberculosis discovered. The amount of tuberculosis found among young adults was also quite high in the hospital group.

With the advent of photo-fluorography it was expected that many general hospitals would take advantage of this economical technique and adopt chest roentgenograms as a routine procedure. This did not occur. As late as 1945, Hilleboe and Morgan (6) reviewed the work of investigators in Ann Arbor, New York, and Chicago where from 1.5 to 2.8 per cent of persons admitted to general hospitals were found to have reinfection type tuberculosis. They concluded that the value of mass radiographic methods in the examination of persons admitted to general hospitals was evident. Furthermore, they hoped that soon all general hospitals would provide routine roentgenographic examinations of the chest as they were already providing routine serologic tests for syphilis.

Plunkett and Mikol, in reviewing the studies of Mills and Stewart (2), Hodges (3), and of Pohle, Paul and Oatway (4) pointed out that these various authors had discovered significant reinfection type tuberculosis in 0.3 per cent to 1.4 per cent of persons who had routine chest roentgenograms on admission to a hospital. The cases discovered were not detected clinically, were unsuspected, and were admitted to the hospitals for reasons other than tuberculosis. They would have remained undiscovered cases of the disease during their hospital residence if a roentgenographic examination had not been made. Each of the three studies reviewed included children, and the surveys were also conducted in hospitals in the Midwest where tuberculosis morbidity and mortality are relatively low.

In their own study in upstate New York, Plunkett and Mikol (1) reported the results of 4,853 routine chest roentgenograms of persons over 15 years of age admitted to general hospitals. As a result of the roentgenographic examinations, 128 patients or 2.6 per cent were found to have reinfection type tuberculosis. In the whole group, 51 individuals, or 1.1 per cent, had significant lesions. In contrast, the relatively similar group of 5,187 persons examined at Erlanger Hospital in the same type of program, yielded 193 patients, or 3.7 per cent, with reinfection type tuberculosis. Moreover, of those found to have tuberculous lesions, 21 per cent were considered to have minimal active pulmonary tuberculosis. It is estimated that of the whole group examined between 1.3 and 1.5 per cent will prove to have clinically significant lesions after more prolonged study. Plunkett and Mikol pointed out the magnitude of the tuberculosis problem in general hospitals. They also stated in part, "In view of the unquestioned value of the x-ray its comparatively low average utilization for chest conditions is regrettable."

Chadwick and Pope (5) in 1942 confirmed the serious risk to student nurses and medical students of unrecognized cases of tuberculosis in hospitals, but they stated further, "General hospitals, also offer a fertile field for case finding. . . . Obviously routine x-ray of all general hospital admissions would do much to uncover unrecognized tuberculosis in the community."

These various authors have clearly emphasized the value of tuberculosis case finding in general hospitals. To date, however, mass radiographic procedures are taken for granted in population groups of other kinds, but there still seems to be some reluctance to use routine chest roentgenography in general hospital populations. Since this particular population group is available without any preliminary work-up like that necessary with all other types of surveys, this reluctance is somewhat difficult to understand. Though it undoubtedly would be of value there is little need, as far as case finding alone is concerned, for the preliminary educational build-up, for the intensive survey campaign and all its contacting and publicity. In fact it appears to the writer that this one population group has been handed to the case finder "on a silver platter."

SUMMARY

The results of clinic, mobile unit, and hospital photo-fluorographic surveys in Hamilton County, Tennessee, have been presented. Data from these surveys have been presented in this early report because of the obvious need for information relative to the value of hospital surveys. Other hospital survey studies have included children, have been made up of a rather small number of adults admitted to hospitals over a short period of time, and have been carried on in areas with low tuberculosis morbidity and mortality rates. The reverse is true in the case of the present study in which significant tuberculous lesions were detected in 3.7 per cent of the persons routinely examined roentgenographically on admission to the hospital.

CONCLUSIONS

1. Insufficient attention has been paid to date to studies showing the value of obtaining routine chest roentgenograms of persons admitted to general hospitals.

2. Comparison of Health Department clinic, mobile unit, and hospital photo-roentgen surveys reveals that the hospital survey finds the highest percentage of cases of reinfection type of tuberculosis.

3. Data from Baroness Erlanger Hospital, Chattanooga, Tennessee, show that 3.7 per cent of persons admitted and routinely examined roentgenographically had unrecognized reinfection type tuberculosis. Between 1.3 and 1.5 per cent of the hospital group routinely examined are believed to have clinically significant tuberculous lesions.

4. The responsibility of the modern general hospital in the tuberculosis case-finding program in the community cannot be over-emphasized in the light of modern case finding techniques.

CONCLUSIONES

La Roentgenofotografía Torácica Sistemática en el Hospital Baroness Erlanger

1. Hasta la fecha se ha prestado insuficiente atención a los estudios que revelan el valor de la obtención de radiografías torácicas sistemáticamente en las personas admitidas a los hospitales generales.

2. La comparación de las encuestas roentgenofotográficas en la clínica del departamento de sanidad, la unidad movible y el hospital revela que el último es el que descubre el mayor porcentaje de casos de tuberculosis tipo reinfección.

3. Los datos del Hospital Baroness Erlanger, de Chattanooga, Tennessee, muestran que 3.7 por ciento de los enfermos recibidos y radiografiados sistemáticamente tenían tuberculosis tipo reinfección no reconocida. Opínase que de 1.3 a 1.5 por ciento del grupo hospitalario examinado sistemáticamente tienen lesiones tuberculosas de importancia clínica.

4. A la luz de las modernas técnicas para descubrimiento de casos, no cabe exagerar la obligación que corresponde al hospital general contemporáneo en las obras de descubrimiento de casos de tuberculosis en la colectividad.

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EDITORIAL

The Necessity for Accurate Evaluation of the Results of Thoracoplasty

Pulmonary resection in the treatment of tuberculosis has become a safer and more widely used procedure than it was a few years ago. The indications for and results of resection are still not clearly defined.

Since the choice of surgical procedures often lies between primary pulmonary resection and thoracoplasty, the need for more accurate and detailed reports of the results of thoracoplasty is becoming increasingly apparent. These reports should be subdivided so as to include an evaluation of the results of thoracoplasty according to the type of disease treated. The age, extent and location of the lesions, the size and type of cavities, and the presence of gross or suspected bronchial lesions are among the factors which undoubtedly influence the results of thoracoplasty to a considerable extent.

Too many published reports of the results of thoracoplasty in the past have failed to take these factors into consideration and have stressed only mortality statistics and the percentage of sputum conversions. A report of the results of thoracoplasty without taking these factors into consideration is analogous to reporting on the results of pneumonectomy without specifying whether the pneumonectomies were performed for carcinoma, for so-called bronchial adenoma, or for pulmonary suppuration.

It is hoped that many more reports on the results of thoracoplasty similar to that of Rubin and Klopstock, which appears in this issue of the Review, will be published in the near future and that authors will classify their cases according to clinico-pathologic groups so that comparison of results from various centers may be possible.

Too often our decision as to the type of surgical procedure to be employed in the treatment of pulmonary tuberculosis is based on impressions of results obtained in cases we have treated recently rather than on a statistical analysis of cases treated over a period of years. For this reason, it is important that those of us who are making such decisions review our thoracoplasty results and classify them according to the type of disease. Although we may not necessarily publish our findings, by making such analyses we will help to clarify the indications for thoracoplasty and primary pulmonary resection in our own minds. Another reason for making our own analyses is that there are bound to be discrepancies between reports of results of thoracoplasty from different centers because of individual variations in the interpretation of roentgenograms, variations in surgical techniques, and differences in the type of patients treated from racial and economic standpoints.

If the results of thoracoplasty can be proved to be poor in a certain type of disease, a trial of pulmonary resection certainly seems justified in that type. On the other hand, if the long term results of thoracoplasty in another type appear highly satisfactory, the use of primary pulmonary resection as an alternative procedure hardly appears justified until more is known concerning the late results of resection.

JOHN D. STEELE

LETTERS TO THE EDITORS

THE EFFECT OF AMMONIUM IONS AND ALIPHATIC AMINES ON THE ABILITY OF VIRULENT MYCOBACTERIA TO BIND NEUTRAL RED

To the Editors of the American Review of Tuberculosis:

It has been shown in an earlier report from this laboratory (Dubos, R. J., and Middlebrook, G., Am. Rev. Tuberc., 1948, *58*, 698) that virulent mycobacteria are capable of binding the basic dye neutral red in the form of its salt even under extremely alkaline conditions. Further analysis of this phenomenon has revealed that binding of the dye can be inhibited by certain surface active agents and cationic substances.

Cultures grown in the presence of high concentrations of asparagine (0.5 per cent) fail to bind neutral red unless they have been washed thoroughly—with 50 per cent methanol, for example—prior to the test. On the contrary, cultures grown in media free of amide and in which asparagine has been replaced by glutamic acid, give a positive neutral red test even without prior washing. We have established, on the other hand, that asparagine exerts its inhibitory effect only if added to the living microorganisms, whereas it fails to interfere with the binding of the dye if added to cell suspensions killed with 2 per cent phenol. These findings suggested that inhibition of binding of neutral red is brought about not by asparagine itself, but rather by some metabolic product of the virulent tubercle bacilli growing in the presence of the amide asparagine.

We have now established that ammonium salts (sulfate or chloride) and a number of aliphatic amines prevent virulent mycobacteria from binding neutral red at alkaline reactions, even when they are used in amounts as small as 1 cc. of 0.001 M solution per mg. of bacterial cells (dry weight). This inhibitory effect exhibits a marked degree of specificity as many other basic substances (aromatic amines, basic peptides and proteins, inorganic cations) have been found to be without effect on the binding of the dye. Among the substances tested so far, atabrine is one of the few possessing some activity in this respect.

Virulent mycobacteria treated with ammonium salts or with the lower aliphatic amines (methylamine hydrochloride, for example) recover the ability to bind the dye after they have been adequately washed, indicating that they combine reversibly with these substances. On the contrary, mycobacteria which have been treated with long chain fatty amines (tetradecylamine, octodecylamine) remain unable to bind the dye even after prolonged washing. It appears likely, therefore, that these long chain compounds become firmly bound to the bacterial bodies by virtue of their lipophilic properties.

Experiments carried out by Dr. Samuel P. Martin and Cynthia H. Pierce, to be published later, have revealed that the ability of virulent mycobacteria to inhibit the migration of polymorphonuclear leukocytes (Allgower, M., and Bloch, H., Am. Rev. Tuberc., 1949, *59*, 562) is neutralized when aliphatic amines are added to the system in concentrations sufficient to neutralize the ability of the microorganisms to bind neutral red.

René J. Dubos
Emmanuel Suter

The Rockefeller Institute for Medical Research
New York, N. Y.
June 27, 1949

TOXIC EFFECTS OF DL SERINE ON VIRULENT HUMAN TUBERCLE BACILLI

To the Editors of the American Review of Tuberculosis:

While studying the effect of amino acids on the growth of mycobacteria and on their ability to bind neutral red under alkaline conditions (Dubos, R. J., and Middlebrook, G., Am. Rev. Tuberc., 1948, *58*, 698) we have observed that dl serine, and to a less extent dl alanine, exert a marked toxic effect (bacteriostatic and bactericidal) on virulent human tubercle bacilli.

The toxicity of these amino acids can be readily demonstrated in a variety of synthetic and semi-synthetic culture media. We have studied its manifestations particularly in a medium consisting of mineral salts, glutamic acid (0.2 per cent), and serum albumin (0.5 per cent). Addition to the medium of the dispersing agent Tween 80 (0.02 per cent) facilitates observation of the results without affecting the outcome of the experiments. The culture media were inoculated with approximately 10^5 living bacilli (from a culture in Tween-albumin medium) per cc. of medium.

Different cultures of mycobacteria vary appreciably in their susceptibility to the toxic effect of dl serine. The most resistant of those tested were three variants of human bacilli, which have become avirulent and have lost also the ability to bind neutral red in alkaline media (H37Ra, H4Ra and JH16Ra). These cultures could grow normally in concentrations of dl serine as high as 0.1 per cent. By contrast three fully virulent strains of human tubercle bacilli were inhibited by adding 0.01 to 0.02 per cent of this amino acid to the same medium.

Surprisingly enough, the bactericidal effect of dl serine can be recognized even at concentrations lower than those required for inhibition of growth. Thus, when the amino acid is added in amounts too small to inhibit bacterial multiplication (0.003 per cent for example), growth at first appears normal both qualitatively (as determined by the morphological appearance and staining characteristics of the bacilli) and quantitatively (as measured by turbidity of the culture). Within a few days, however, autolytic changes become manifest (loss of acid fastness and decrease in opacity) and subcultures in new media free of serine reveal that a large percentage of the bacilli fail to grow even after prolonged incubation. It is of interest that, simultaneously with this sterilizing effect of dl serine on growing cultures of virulent human tubercle bacilli, other cellular alterations take place which bring about a loss of ability of the microorganisms to bind neutral red in an alkaline environment.

René J. Dubos

The Rockefeller Institute for Medical Research
New York City, N. Y.
June 27, 1949.

THE INTRAVENOUS ADMINISTRATION OF P-AMINOSALICYLIC ACID[1]

To the Editors of the American Review of Tuberculosis:

A serious objection to p-aminosalicylic acid as a chemotherapeutic agent for tuberculosis is the nausea and vomiting patients experience when the drug is administered by

[1] This study was supported by a grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

mouth. There is a wide variation in the amount of the drug which each individual patient can tolerate. Some complain only of anorexia on a daily dose of 10 to 15 Gm.; others have severe nausea and vomiting on as little as 5 or 6 Gm.

In view of the fact that parenterally administered PAS in two subcutaneous doses per day produced favorable results on the course of tuberculosis in experimental animals, it was decided to explore the feasibility of the parenteral administration of the drug to patients.

An isotonic solution of sodium p-aminosalicylic acid adjusted to a pH of 7.35 is not irritating to tissues and can be given either subcutaneously or intravenously without discomfort. To prepare such a solution, suspend 22 Gm. (144 milli equivalents) of powdered PAS in approximately 100 cc. of pyrogen-free water. Dissolve 7.6 Gm. of sodium carbonate in 100 cc. of pyrogen-free water and add it slowly and with constant stirring to the PAS suspension. Using a glass electrode pH meter, adjust the final pH of the solution to 7.35 by adding, drop by drop, additional sodium carbonate solution, and then sterilize by passing through a Seitz filter. Dilute the filtrate to 1,000 cc. with sterile pyrogen-free water to obtain a clear amber solution. This preparation, if kept in a refrigerator, keeps for many weeks without deterioration.

Patients have received 500 cc. of this solution intravenously daily for up to six weeks without complaining and without sclerosis of the veins. More recently, intravenous solutions containing 33 Gm. of PAS per liter have been given without ill effects. If the solution is given too quickly and blood levels of more than 40 mg. per 100 cc. are produced, then the patient does become nauseated.

Liver function studies carried out before as well as after a course of intravenous PAS therapy did not show any evidence of liver damage in the small number of patients so far treated in this manner. Prothrombin times had a tendency to drop, but none went below 70 per cent of normal.

It remains to be seen if this has an influence on promoting pulmonary hemorrhage.

WILLIAM R. BARCLAY

THE DEPARTMENT OF MEDICINE
UNIVERSITY OF CHICAGO MEDICAL SCHOOL
CHICAGO, ILLINOIS
June 30, 1949.

Strachimer A. Petroff

1883-1948

The late Strachimer A. Petroff was the last of the brilliant group of research men who were associated with Dr. E. L. Trudeau after his founding of the Trudeau Sanatorium, and who made up the famous "Trudeau Group." Lawrason Brown, E. R. Baldwin, Leroy U. Gardner, Fred Heise, Homer Sampson, and S. A. Petroff were all men who grew up around Dr. E. L. Trudeau and who made the name of Trudeau famous in the world of tuberculosis in the first third of the century when the solid ground-work of the struggle against tuberculosis was being laid.

Doctor Petroff was born in Varna, Bulgaria, in 1883 and studied at the University of Sofia. In 1900 he came to the United States as part of a "grand tour" of the world to complete his education. An early evidence of his independence of thought, which was later so fruitful to science, was a long-range political argument with his family. This resulted in cutting off all ties and leaving himself stranded in a foreign land with practically no knowledge of English and no means of support. Fortunately, as it turned out, he then "broke down" with tuberculosis and came to Trudeau Sanatorium. Here he attracted the attention of Doctors Lawrason Brown and E. L. Trudeau, who put him to work in the Research Laboratory and in 1907 put him on the Research Staff. In 1912 he married Mary Fears Gilmer, a nurse who was a fellow patient at Trudeau. This was an important turning point in his career. Her devotion to him and to his work proved to be of inestimable value to him, and their long and happy marriage contributed largely to his success. In 1921 he succeeded Dr. E. R. Baldwin as Director of the Research Laboratory at Trudeau Sanatorium where he remained until 1936. In 1937 he accepted the Directorship of the Bacteriological Laboratory at Sea View Hospital, Staten Island, N. Y., the largest tuberculosis hospital in the country, where the wealth of material available gave ample scope to his tremendous capabilities. This post he held until his retirement because of ill health to his home in Greenville, South Carolina, in 1946.

Doctor Petroff's contributions to science, and more particularly to tuberculosis, are listed in the more than one hundred articles that he published during his nearly forty years of active research work. He was a mechanical genius. Various pieces of laboratory apparatus: needles, slide holders, media, et cetera, are a few of the things he developed. In 1927 as co-author with Doctors Baldwin and Gardner he published *Tuberculosis—Bacteriology, Pathology and Laboratory Diagnosis*, a most valuable contribution.

His work on the dissociation of the tubercle bacillus had an important and far-reaching effect. It is difficult today to recall the enormous excitement in the world of tuberculosis workers elicited by the Lübeck disaster and the subsequent trial and world discussion of BCG. Doctor Petroff, because of his outstanding work in dissociation of the tubercle bacillus and of BCG was called by the

German authorities to testify in the Lübeck trial and his testimony against BCG is still debated.

Doctor Petroff was widely honored during his lifetime. In 1923 he received a Doctorate of Philosophy from Columbia University where he had studied under the late Dr. Hans Zinnser. He received an honorary Doctorate of Science from Colgate University in 1932. He was an active member of the American Society of Bacteriologists, the Society of Experimental Biology and Medicine, the Society of Immunologists, and the American Editors and Authors Association.

He was a member of the National Medical Advisory Board in the First World War, and in 1928 a Special Member of the International Board of Health of the League of Nations. From 1931 to 1933 he was a member of the National Research Council.

In paying honor to Doctor Petroff at his passing, we not only honor a brilliant scientist but again pay tribute to that group of great men of which he was a part and to whom we in tuberculosis owe so much, the "Trudeau Group."

HENRY W. LEETCH

George Chambers Anglin

1890-1948

Following a full day's medical duties on Tuesday, April 16, 1948, Doctor Anglin suffered an almost immediately fatal heart seizure during that night.

Born in Ireland, Doctor Anglin came to Canada in 1907, and was graduated from the University of Toronto in 1914. He served in the R.A.M.C. from 1915 to 1918. He continued as Director of the Chest Clinic at Christie Street Military Hospital, and during the Second World War was Chest Consultant for the three services in the Toronto Military District. For his services in the same capacity to the Norwegian Air Force he was signally honored by the King of Norway.

He was a member of the Staff of the Toronto Hospital and enjoyed a large consulting practice in allergic and chest diseases, with perhaps his deepest interest in tuberculosis. He had long been a member of the Trudeau Society and active in the Canadian Tuberculosis Association and the Laennec Society of Ontario. In addition to his Canadian affiliations, he was a member of many other medical bodies, including the American College of Physicians, the American College of Chest Physicians, American Academy of Allergists, and the American Board of Internal Medicine. He was a member of the Senate of the University of Toronto from 1944, President of the Medical Alumni Association of the University in 1945–1946, and included among his activities those of the Church and philanthropic bodies.

The profession in Canada has suffered a severe loss in his untimely death.

HAROLD I. KINSEY

BOOKS

JOHN FRANCIS: *Bovine Tuberculosis: Including a Contrast with Human Tuberculosis. Pp. 220 (Foreword by J. R. M. Innes), 1947, Staples Press, Ltd., London, Price, 25s.*

The program for the eradication of tuberculosis among cattle in the United States was initiated in 1917. The results of this tremendous undertaking in the control of a major infectious disease have been amazingly good, and constitute a notable conquest of an animal disease of great economic and public health importance. However, physicians and others concerned with the epidemiologic aspects of tuberculosis in human beings often lose sight of the fact that in certain other parts of the world tuberculosis of cattle still remains a tremendous economic burden on agriculture and a constant threat to human health.

Francis' book, which is the subject of this brief review, should serve as a reminder that bovine tubercle bacilli are capable of severe and even fatal infections in human beings and that tuberculosis in man cannot be eliminated or even satisfactorily controlled unless the disease in cattle is subjected to measures that will eventually lead to its eradication. Since there has been no recent adequate review of bovine tuberculosis on a world-wide basis, Francis has accomplished an important task in providing a great mass of information pertaining to the disease in its natural and in other susceptible hosts. In addition, the detection and control of the infection in cattle are considered.

The subject matter of the book is divided into six major subdivisions. These include the incidence of tuberculosis of cattle and the economic loss occasioned by the disease; a consideration of the pathogenesis of bovine tuberculosis in the natural host (this is prefaced by a brief discussion of the important differences between the development of tuberculosis in human beings and in different species of animals); tuberculosis of bovine origin in man; detection of tuberculous cattle by tuberculin and by other means; vaccination of cattle with BCG and with the vole bacillus; and lastly, the control of bovine tuberculosis.

A valuable feature of the book is the well-written summary that concludes each subdivision. This idea has been extended to an over-all summary of the entire book, in which the author has succeeded in condensing into four and one-half pages the most important facts which his admirable review has revealed.

Francis concludes that the incidence of tuberculosis among all the cattle of Great Britain is between 17 and 18 per cent. However, he states that the incidence of the disease is higher among dairy cattle, where the average incidence is about 25 per cent. The data indicate that the incidence increases with the extension of age; in infected herds, 40 per cent of the animals five to six years of age may be infected. (By comparison, at present the incidence of tuberculosis in the cattle population of the United States is less than 0.5 per cent.)

As to the occurrence of bovine tubercle bacilli in the milk in Great Britain, Francis states that "about eight per cent of raw churn milk and nearly all of the 3,000 gallon tanks, in which raw milk is frequently brought to our large cities, contain tubercle bacilli." Francis believes that in Great Britain 5 per cent of all human deaths due to tuberculosis are due to infections caused by the bovine type of the tubercle bacillus. Of children less than 5 years of age who die of tuberculosis, the incidence of infection due to bovine tubercle bacilli is considered to be 30 per cent. The extension of pasteurization to include all milk used for human consumption would at least protect human beings from this infection.

Since 1935 the veterinary profession and dairy owners of Britain have made a creditable beginning in establishing "attested" or tuberculosis-free herds. It is estimated that at the present time approximately 10 per cent of the cattle in Great Britain are in herds "attested" as being free of tuberculosis. Perhaps when the true significance of tuberculosis of dairy cattle is fully appreciated by the consumer of milk and dairy products the final conquest of bovine tuberculosis in Great Britain will not be long delayed.

Francis has contributed to the solution of the problem by assembling the facts. What use is made of them will depend on how insistent the British public becomes in demanding the correction of the shocking evils that perpetuate the distribution of misery and death in milk containers.

Francis completes his review by listing 400 selected references from the world's literature. This is followed by a useful and apparently correct and adequate index.

This book is truly an indispensable reference for physicians, public health workers, and veterinarians who are expected to be informed concerning an extremely important disease of cattle which so long as it exists constitutes a menace to human welfare. The book should focus attention on the fact that tuberculosis is a disease of many different species and that a heterologous infection can be as important to the human patient as a homologous one.

W. H. FELDMAN

ROBERT COOPE: *Diseases of the Chest, Second Edition, Pp. 541, The Williams & Wilkins Company, Baltimore, 1948, Price, $7.50.*

This book is written for medical students and general practitioners. It presents a well-balanced combination of anatomical, physiological, and pathological considerations with clinical aspects of diseases of the chest. The reader obtains a well-rounded picture of respiratory diseases by equal emphasis of the above stated factors. Considerable attention is paid to the social and economic factors of respiratory diseases. The discussion of the social aspects of tuberculosis, for instance, is well worth being read not only by the general practitioner but also by every worker in this field. The book contains only a small number of radiograms as the author takes the viewpoint that radiology should be taught in hospital practice in relation to patients studied by the student himself. The few chest films included at the end of the book are of good technical quality.

Some therapeutic chapters are not quite up to date. Significant advances, such as the antibiotic treatment and excisional therapy of tuberculosis, are not mentioned. Beryllium poisoning and histoplasmosis, diseases more intensively studied in this country in recent years, should be included in future editions.

The reading of the book is made easy by the vivid and stimulating style of the author. The medical student will find this book the logical continuation of his preclinical training in the anatomy and physiology of the respiratory tract while the general practitioner should welcome the opportunity to refresh his knowledge in this field by the thorough presentation of the various factors involved in each disease.

HANS ABELES

ESTHER LUCILE BROWN: *Nursing For The Future: A report prepared for the National Nursing Council. Pp. 198, Russell Sage Foundation, New York, N. Y., 1948, cloth, $2.00.*

This report is the omega and alpha of an examination of the question of who should organize, administer, and finance *professional* schools of nursing. The study completes

part of one sector of the program for nationwide action in nursing proposed by the National Nursing Council as an outgrowth of cooperative activity of nursing organizations during World War II. The study was undertaken in the hope that impetus might be provided for redirection of effort.

"The first, and most important, basic decision made during preliminary discussions was to view nursing service and nursing education in terms of what is best for society—not what is best for the profession of nursing as a possibly 'vested interest'."

The director of the study, Dr. Esther Lucile Brown, was released for this important work from her position as Director of the Department of Studies in Professions of Russell Sage Foundation. In 1940 she had written a book, *Nursing as a Profession*, and had also participated in studies to determine how "education for an essential profession can be molded to meet the present needs of society." Dr. Brown's rich background has enhanced the value of her report which is an outstanding contribution to nursing as well as to society. The study was financed in part by a grant from the Carnegie Corporation of New York.

In the first two chapters of the report the author vividly portrays the extension of health services and the implications of these changes for the nursing of the future.

She believes the answer to the problem of obtaining a supply of nursing care that is quantitatively and qualitatively sufficient lies in answers to the questions: What kinds of *nursing functions* need to be performed? Can persons be found and prepared to fulfill these *functions* effectively, whether they be graduate nurses or not?

In discussing the future role of the professional nurse, Doctor Brown recommends that the term professional when applied to nursing education and to nurses be restricted to those schools and those nurses able to meet certain defined standards and that nursing make a matter of first importance the examination of all schools, designating and publishing a list of those which meet standards for accredited professional schools.

The final chapters are devoted to a discussion of education for practical and graduate bedside nurses and resources for the future.

The six national nursing organizations have accepted in principle the recommendations in the report *Nursing for the Future* and are working together to promote study and action by lay and professional groups which will help to solve the problems and provide the kind of nursing we all seem to want.

KATHARINE G. AMBERSON

THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

Edited by LAWRENCE B. HOBSON

VOLUME 60 SEPTEMBER, 1949 ABST. No. 3

CLINICAL STUDIES, TUBERCULOSIS

Bronchi in Primary Childhood Tuberculosis.—Three causes of epituberculosis have been proposed: nontuberculous pneumonia, true tuberculosis, and absorption collapse due to pressure of tuberculous nodes. Thirty children were examined bronchoscopically. These included 18 with active primary tuberculosis associated with sharply outlined radiographic shadows of a lobar or segmental type but without mediastinal or tracheal shift; this is the "classical" picture of epituberculosis. In 10 others, the above findings were noted plus a mediastinal shift; this included 2 cases with obstructive emphysema. In the remaining 2, there was bronchiectasis complicating healed tuberculosis. The right side was involved more often than the left. The various bronchial changes were arranged by groups. In type I (9 cases) there was localized bulging of hyperemic mucous membrane. The process sometimes partially occluded the middle lobe bronchus or a branch of the upper lobe bronchus. Thick mucus could intermittently complete the obstruction. This lesion was caused by external pressure of tuberculous nodes. In type IIa (3 cases), the changes of type I were found and in addition there were yellow, glistening, slightly raised areas under the mucous membrane, representing caseous nodes which were "pointing." In type IIb (2 cases), the bulge was more circumscribed and represented a tuberculoma, biopsy of which showed tuberculous tissue. In type IIIa (7 cases), there was an area of ulceration covered by granulation tissue. It is not certain whether a node had evacuated or was still "boring." In type IIIb (5 cases), the bronchus was filled with friable granulation tissue. In type IV (2 cases), no abnormality was seen. In 15 of the 26 cases with positive findings, the carina was widened. In the 2 cases of healed tuberculosis, the findings were a narrowing of the entrance to the middle lobe bronchus in one case and a distortion of the right lower lobe bronchus in the other. The conclusion is that epituberculosis really is absorption collapse secondary to bronchial compression or erosion by tuberculous nodes.—*Bronchoscopic studies in primary tuberculosis in childhood, J. N. Hutchison, Quart. J. Med., January 1949, 18: 21.*—(*A. G. Cohen*)

Depression of Tuberculin Sensitivity.—Depression of skin sensitivity to tuberculin has been reported previously in patients critically ill with tuberculosis. This study was carried out, in contrast, on patients critically ill with diseases other than tuberculosis as subsequently shown by autopsy examination at the Kansas City General Hospital. Only white patients were tested. The tuberculin used was PPD-S containing 0.0001 mg. in 0.1 cc. Histoplasmin prepared by the Public Health Service was employed. The usual proportion of positive reactions to tuberculin and histoplasmin was determined by examining 4,555 apparently healthy persons of all ages. This expected proportion was then compared statistically with the observed reactions in 305 critically ill patients. Among the men, the observed number of reactions to tuberculin among the ill was identical with the expected number for persons between 20 and 39 years of age; between 40 and 59 years the observed number was only 31 per cent of

the expected; between 60 and 79 years, it was 24 per cent, and it fell to 10 per cent in the group over 80 years. Statistics were similar for the women. The results with the histoplasmin reactions were similar except that even between 20 and 39 years the observed reactions among the ill were only 76 per cent of the expected. Almost one-half of those who were insensitive and later recovered showed positive skin tests when they began to improve. The evidence suggests that the depression is nonspecific with respect to the antigen used and the cause of the illness.—*Depression of tuberculin and histoplasmin sensitivity associated with critical illness, M. Furcolow, M. Engel, & I. Bunnell, Pub. Health Rep., October 1, 1948, 63:* 1290.—(*S. Hadley*)

Tuberculoma of the Lung.—Tuberculoma of the lung is defined as "pseudo-tumoral" pulmonary tuberculosis giving spherical, well-circumscribed densities on roentgenograms; usually the sputum contains no tubercle bacilli. Pathologically these tuberculomas do not represent a real entity. Thus, 3 lung specimens removed by lobectomy or pneumonectomy showed 2 different types of disease. In 2 cases the tuberculoma had formed by the confluence of areas of tuberculous bronchopneumonia and of tubercles which were partly or entirely caseated. These were mixed with dense interstitial fibrosis. The third tuberculoma, a round density in the right lower lobe, consisted anatomically of an entirely caseated mass. The caseous material was arranged in concentric layers, each surrounded by a thin fibrous capsule. The origin probably was a central node which gradually enlarged by progressive eccentric caseation. This is considered the more common pathological substratum of tuberculomas.—*Étude anatomique et pathologique de tuberculomes du poumon, P. Galy, M. Berard, & J. Dumarest, Rev. de la tuberc., 1948, 12:* 678.—(*V. Leites*)

Lung Resection for Tuberculosis.—Recent improvements in technique have rendered the surgical removal of tuberculous lung tissue a somewhat safer procedure than formerly although complications still occur. Since Friedlander's first successful upper lobe removal in 1935, many thoracic surgeons have attempted resections but it is still very difficult to determine the value of such operations. Undoubtedly the results in some cases have been remarkable; many patients have been promptly restored to health without the long and tedious period of convalescence which was necessary after collapse therapy. From 1935 to 1940, the results were discouraging; the mortality following operation varied from 30 to 60 per cent. Beginning about 1942, the results improved as important changes in operative procedure were made, including separate ligation of the blood vessels of the lung stem, suturing and pleuralization of the bronchus, modern anesthesia, and greater use of bronchoscopy, penicillin, and streptomycin. The author usually has used the lateral position with the affected side down and has employed general anesthesia in a closed circuit. When many firm adhesions were present, he has entered extrapleural areas. Of a total of 12 cases, 2 have died and 6 are well, one for more than four years. He removed the apex of the lung for small residual cavities after thoracoplasty in 4 patients, 2 of whom are alive and working. Other surgeons who have resected lung tissue for tuberculosis report mortalities from 5 to more than 50 per cent. The deaths have been due to spread of the disease in the other lung, to empyema, to miliary tuberculosis, to bronchial fistula, and to meningitis. It seems that the value of removal of tuberculous foci by meticulous operative technique has been established but the serious complications and the effects on pulmonary function must be kept in mind. Indications for pneumonectomy, provided the other lung is free from disease, include stenosis of the main bronchus, dilatation of the smaller bronchi, and persistent cavity. Lobectomies are done for basal cavities, tuberculomas, stenosis of the lobe-bronchus, and cavities of the upper lobe which cannot be eliminated by thoracoplasty. If there is any chance that a thoracoplasty may lead to

healing of the lesion without resection, the latter procedure should be postponed.—*Les opérations d'exérèse dans le traitement de la tuberculose pulmonaire, Monod, O., Le Poumon, November, 1948, 4: 327.*—(*A. T. Laird*)

Tuberculous Empyema.—The incidence of tuberculous empyema has been increasing since the introduction of artificial pneumothorax. Tuberculous empyema follows artificial pneumothorax in 3 to 20 per cent of the cases and has a mortality rate of 28 to 60 per cent. Treatment includes (*1*) aspiration and replacement with air only, (*2*) aspiration and irrigation, (*3*) oleothorax, (*4*) thoracotomy, and (*5*) thoracoplasty. It seems best to remove the pus and irrigate the cavity with Dakin's solution to avoid fistula formation. Twenty-three cases of tuberculous empyema were thus treated with aspiration and irrigation. The empyema followed artificial pneumothorax in 14 cases, effusion in 8 cases, and tuberculous spontaneous pneumothorax in one case. There were 7 cases of minimal pulmonary tuberculosis, 8 cases of moderately advanced, 5 cases of far advanced disease; and 3 without pulmonary lesions. At the end of treatment, 12 patients had their lungs fully expanded and their cavities obliterated, 2 required thoracoplasty, 6 pneumothorax, and one an oleothorax; 2 cases died during treatment. Nineteen patients were followed one to eight years after treatment; 17 were living and working, one was being treated for a pulmonary lesion, one had died from tuberculosis.—*Treatment of tuberculous empyema by aspiration and Dakin's solution irrigation, B. H. Y. T'ang, Chinese M. J., April, 1948, 66: 205.*—(*L. Hyde*)

Chest Wall Tuberculosis.—Cold abscesses or chronic discharging sinuses of the chest wall were found in 8 patients of whom 7 had minimal tuberculous lesions in the lungs. Five had sinuses of the chest wall. The belief that tubercle bacilli are carried to the chest wall via the lymphatics was supported by finding tuberculous lymphadenitis in pathologic sections from 6 patients. The disease should be suspected in any relatively painless, persistent swelling of the chest wall, even if roentgenograms show no bony changes. The diagnosis is established only by demonstrating tubercle bacilli or by finding typical tubercles in the tissues. Removal of the abscess, sinus, and involved bone or cartilage cured 4 of the 8 patients, improved 2, and failed to help the remaining 2.—*Tuberculosis of the chest wall, C, Huang & M. Stone, Chinese M. J., March, 1948, 66: 125.*—(*L. Hyde*)

Tuberculous Abscess following Penicillin Injection.—A patient developed a tuberculous abscess at the site of penicillin injections. No other tuberculous foci were demonstrated in the body. The lesion is believed to have been hematogenous in origin, though introduction of infection through the needle is a remote possibility.—*Tuberculous abscess at site of penicillin injection, G. B. Forbes & F. G. St. C. Strange, Lancet, March 19, 1949, 1: 478.*—(*A. G. Cohen*)

Clinical Studies, Nontuberculous Diseases

Intracellular Bodies in Sarcoidosis.—In 1917, J. Schaumann described the occurrence of double-contoured, stratified, and sometimes calcified bodies in practically all of the organs from some patients with sarcoidosis. Most authors have considered these bodies to be the products of degeneration of elastic fibrils impregnated with calcium and iron salts. Metchnikoff reported the production of similar bodies by the inoculation of tubercle bacilli into the Algerian gerbil, an animal resistant to tuberculosis. In view of this observation, Schaumann advanced the opinion that tubercle bacilli can be transformed into these structures. The author considers the stratified bodies in Boeck's sarcoidosis to be partly crystalline, globulin precipitates in the cytoplasm. He denies that they are the products of transformed tubercle bacilli and interprets the morphologic lesions in this disorder as representing a serological, hyaline (paramyloid) precipitation having as its starting point a globulin precipitate (allergic hy-

perglobulinosis) in the reticulo-endothelial system. It is highly probable that these precipitates behave as foreign bodies. The hyperglobulinotic reaction is interpreted as expressing an especially high degree of immunity and this explains the occurrence of stratified bodies in Metchnikoff's inoculation experiments referred to above.—*The nature of the double-contoured and stratified intracellular bodies in sarcoidosis (Boeck-Schaumann), G. Teilum, Am. J. Path., January, 1949, 25: 85.—(J. S. Woolley)*

Serology of Sarcoidosis.—It was found that the serum of patients with sarcoidosis could modify or even neutralize the ability of Old Tuberculin (OT) to evoke a typical skin reaction when 9 parts of serum were added to one part of a 1:1,000 dilution of OT. As controls, sera were used from apparently well individuals who showed either a positive or negative Mantoux reaction. Two tuberculin injections were made on the arm of each subject, one containing serum from a control and the other from a patient with proved sarcoidosis. The sera of the sarcoidosis cases almost always showed tuberculin neutralizing powers; occasionally one did not. On the other hand, only an occasional control showed these properties. Thus, the test is not valid for routine diagnostic purposes. The neutralizing powers were weaker after natural remissions, surgical removal of foci, or roentgen therapy. The test was less effective when used on patients with active tuberculosis. The sera were fractionated and it was found that the neutralizing power is in the gamma globulin. Normal gamma globulin does not possess this power. The factor is destroyed by heating at a temperature of 65°C. for one hour. It is not affected by soya bean antitrypsin (cf. fibrinolysin).—*A tuberculin-neutralising factor in the serum of patients with sarcoidosis, A. Q. Wells & J. A. H. Wylie, Lancet, March 12, 1949, 1: 439.—(A. G. Cohen)*

Bronchogenic Carcinoma.—Primary bronchogenic carcinoma was proved in 131 cases observed between 1940 and 1946. The incidence of bronchogenic carcinoma is increasing absolutely and relatively. Of the 131 patients, 125 were men, 6 were women. Eighty-two patients (62.5 per cent) were between the ages of 50 and 70. One hundred eleven (84.7 per cent) died within eighteen months after the diagnosis had been made. In 63 patients the carcinoma was found in the right lung, in 68 cases in the left lung. The carcinoma was of the squamous cell variety in 114 cases and of the adenomatous type in 14. The most important symptoms are: cough, present in 100 patients (76.3 per cent); thoracic pain, in 82 (62.5 per cent); sputum, dyspnea, hemoptysis, loss of weight, wheezing, pulmonary hemorrhage, paralysis of the vocal cords, dysphagia, convulsions, or paralysis of central origin. The roentgenogram is the most valuable single means of obtaining an early presumptive diagnosis. Bronchoscopy should be performed in all cases of suspected bronchogenic carcinoma. Further means of diagnosis are: aspiration biopsy, exploratory thoracotomy, and cytologic study of bronchoscopically removed secretion. The following methods of treatment are used: (*1*) bronchoscopic removal of tissue with forceps and/or with electrocoagulation; (*2*) irradiation; (*3*) surgical removal of the involved lung.—*Primary bronchogenic carcinoma: Correlation of recent literature with one hundred and thirty-one proved cases, J. J. O'Keefe, Arch. Int. Med., October, 1948, 82: 345.—(G. C. Leiner)*

Sputum Smears for Carcinoma.—Two hundred cases in which a diagnosis of carcinoma was made on the basis of examination of smears of sputum or bronchial secretions were analyzed. In 190 cases a final diagnosis of primary or metastatic pulmonary carcinoma was made. In 4 cases a carcinoma in the esophagus, larynx, or trachea was demonstrated. In 4 cases the examination was proved to be falsely positive. In the remaining 2 cases the final diagnosis was uncertain. Exfoliated carcinoma cells in sputum or bronchial secretions provided the only preoperative microscopic evidence of cancer in 29 of 74 cases of bronchogenic carcinoma in which surgical

exploration was carried out. Sputum and bronchial secretions have proved equally satisfactory in the cytologic diagnosis of cancer of the lung; bronchial secretions have the advantage of better localization of the lesion. If no sputum is available or if no bronchial secretions can be aspirated, bronchial washing may be required.—*Diagnosis of carcinoma of the lung, the value of cytologic study of sputum and bronchial secretions, L. B. Woolner & J. R. McDonald, J. A. M. A., February 19, 1949, 139: 497.*—(*H. Abeles*)

Thymoma.—A patient who was suspected of having tuberculosis subsequently developed a right mediastinal opacity and a bloody pleural effusion. Autopsy revealed a light yellow tumor in the anterior mediastinum compressing the right bronchus, lung, heart, and larger blood vessels. There were no metastases to regional lymph nodes. Microscopic examination of the tumor showed it to to be mostly necrotic. The tumor cells were polymorphic with many large reticulum cells, sometimes arranged in trabeculae resembling deformed Hassall's corpuscles. Mitotic figures were rare.—*Thymoma: Report of a case, S. C. Pan, C. S. Chih, & Y. P. Chien, Chinese M. J., May, 1948, 66: 257.*—(*L. Hyde*)

Eosinophilic Granuloma of Rib.—A man aged 46 was found by routine roentgenogram to have a sharply defined area of increased density in the left tenth rib. There was no blood eosinophilia. Seven years later, there was no change in size or appearance of the lesion. In the eighth year, he developed persistent pain in the region of the swelling and one year later it was removed. Histological examination showed an eosinophilic granuloma. Review of the literature shows reports of 46 previous cases ranging in age from one month to 39 years. Most were in children. The present patient is the oldest in whom the condition has been reported.—*Eosinophilic granuloma of rib, A. R. Grant, R. K. House & W. B. Crandell, New England J. Med., April 7, 1949, 240: 541.*—(*A. G. Cohen*)

Scoliosis and Cardiac Failure.—A 19 year old white girl with scoliosis due to anterior poliomyelitis, first noted at the age of 5, died from cardiorespiratory insufficiency. The following explanation is made: "Important effects of thoracic deformity are to limit pulmonary ventilation, to impede the pulmonary circulation, and to alter respiratory fluctuations in blood flow. Increased ventilatory effort, tachycardia, and right ventricular dilatation and hypertrophy are thereby induced. If these responses can be considered compensatory, they are inadequate to permit normal development and activity and they ultimately fail completely. Treatment is largely preventive, and begins with prevention or correction of the thoracic deformity itself."—*Scoliosis and cardiac failure, W. T. Hill, Am. Heart J., March, 1949, 37: 435.*—(*G. C. Leiner*)

Pneumonia in Hemolytic Anemia.—A 20 year old woman died with an acute hemolytic anemia of unknown cause, pneumonia in the right lower lobe, acute nephritis, and thrombophlebitis of the left iliac vein. The autopsy examination showed disseminated fibrinoid arteritis, nephritis, and an atypical pneumonia of the right lower lobe. The pneumonia was characterized by the presence of a peculiar interstitial infiltrate, consisting of plasma cells, lymphocytes and large mononuclear leukocytes. Many of the alveoli contained fibrin. Fibrin plugs were seen in the alveolar capillaries and there were intra-alveolar hemorrhages. There were numerous megakaryocytes in the alveolar capillaries. No microorganisms were found.—*Acquired acute hemolytic anemia of unknown cause: Report of a case with fibrinoid arteritis, atypical pneumonia and lower nephron nephrosis, L. J. Rather, Arch. Int. Med., December, 1948, 82:* 578.—(*C. G. Leiner*)

Lymphogranuloma Venereum.—An 18 year old Negro complained of malaise, anorexia, cough, precordial pain, loss of weight. On physical examination a pericardial friction rub was heard and a single enlarged superclavic-

ular lymph node was found. A chest roentgenogram showed enlargement of the hilar lymph nodes. The Frei test and the complement fixation test for lymphogranuloma venereum were positive. Histologic study of the supraclavicular lymph node showed the characteristics of lymphogranuloma venereum. The specific virus was isolated from this node.—*Lymphogranuloma venereum in a patient with mediastinal lymphadenopathy and pericarditis: Isolation of the virus from the supraclavicular lymph node, W. H. Sheldon, M. J. Wall, J. DeR. Slade, & A. Heyman, Arch. Int. Med., October, 1948, 82: 410.—(G. C. Leiner)*

Epidemic Pleurodynia.—Between July and October, 1947, 114 cases of epidemic pleurodynia were observed at the Boston City Hospital. The age of the patients was from 3 to 69 years, 80 per cent being less than 30 years old. There were 77 men and 37 women. The onset of the illness was sudden in most cases with pain as the first symptom. Pain only in the chest occurred in 55 patients, in the chest and in the abdomen in 42, only in the abdomen in 16, only in the lumbosacral region in one. Headache was common; cough, anorexia, diarrhea, and chills also occurred. The patients had fever between 99° and 104°F. Other findings were splinting of the chest, pleural friction rub, tenderness of abdomen or chest, slight to moderate enlargement of one or more groups of lymph nodes, pharyngitis, and tonsillitis. Roentgenographic examinations of the chest revealed no abnormalities. Leukopenia with eosinophilia was observed in some cases. Pericarditis, orchitis, and involvement of the central nervous system appeared as complications. The administrations of penicillin and streptomycin had no effect on the course of the disease. Attempts to isolate the etiologic agent gave no results.—*Epidemic pleurodynia: Clinical and etiologic studies based on one hundred and fourteen cases, J. F. Finn Jr., Th. Weller & H. R. Morgan, Arch. Int. Med., March, 1949, 83: 305.—(G. C. Leiner)*

Chronic Bronchitis.—Chronic bronchitis is characterized by cough, expectoration, and dyspnea. These symptoms may be constant or intermittent. The author believes that in most cases the condition is really a mild form of asthma. In older people, left ventricular failure must be ruled out. Other conditions from which it must be differentiated are sinusitis, bronchiectasis, cystic disease, abscess, carcinoma, and tuberculosis. Asthma is the essential element in all cases and is often allied with vasomotor rhinitis. There are many children who are prone to bronchitis; this later wears off unless the individual is subject to unusual stresses, such as military service. Generalized emphysema is the end result and is the proof of the previous existence of bronchial spasm. Infection is most often secondary. Therefore, given a patient with so-called chronic bronchitis, the first step is to exclude other diseases. The purulent infection should be considered as secondary and treated with antibiotics. Then the primary condition must be treated with antispasmodics and breathing exercises.—*Chronic bronchitis, W. A. Lister, Lancet, April 30, 1949, 1: 719.—(A. G. Cohen)*

Tropical Eosinophilic Asthma.—Tropical eosinophilic asthma is characterized by chronic bronchitis with nonseasonal nocturnal paroxysmal cough, dyspnea, leukocytosis, and high eosinophilia. The disease may last for many years. The etiology is unknown. Administration of arsenicals causes aggravation of symptoms which is followed by complete recovery. Three cases of tropical eosinophilic asthma have been reported previously. Two new cases are described in this paper and a third case is mentioned in a note. All patients had been in the South Pacific area.—*Tropical eosinophilic asthma, report of two cases, I. Fond & P. Ravenna, Arch. Int. Med., November, 1948, 82: 422.—(G. C. Leiner)*

Fluids for Bronchial Asthma.—Intravenous use of dextrose is indicated in the severe status asthmaticus patient in whom fluids by mouth

are not well tolerated or in those patients in whom orally administered fluids reflexively produce severer asthma. Contraindications to the use of dextrose are minimized by the use of a 5 per cent solution in distilled water. Not more than 500 cc. per hour and 3,000 cc. in a twenty-four hour period should be administered.—*Intravenous use of fluids in bronchial asthma, J. M. Sheldon, J. A. M. A., February 19, 1949, 139: 506.*—(*H. Abeles*)

Pulmonary Complications of Dysphagia.—Mechanical dysphagia complicated by pulmonary lesions was present in 39 cases from the literature and in 9 from the author's series. This was caused by the aspiration of esophageal contents into the bronchial tree. The mechanism varied with different lesions. Carcinoma of the upper third of the esophagus was very likely to produce dysphagia, especially when there was vocal cord paralysis. Aspiration was less likely with neoplasms of the lower two-thirds. The most frequent lesion complicated by pulmonary changes was achalasia of the cardia, aspiration occurring only during sleep. Pharyngeal diverticulum was also a frequent cause. Aspiration of esophageal contents differs from ordinary aspiration from the upper respiratory tract and mouth in that it occurs in small spills and the aspirated material is less likely to contain organisms. The pulmonary lesions observed were lung abscess in 18 cases, bronchiectasis in 6, fibrosis in 10, lipoid pneumonia in 4, "pneumonitis" in 8, and collapse in 2. There was no hard and fast boundary between these lesions; one type often merged into the other. Tracheobronchitis often preceded the appearance of frank pulmonary lesions. "Pneumonitis" in this article refers to nonspecific inflammation of the lung; it often occurred separately or in association with fibrosis or lung abscess. The aspirations responsible were minimal, sporadic, and of short duration. Pulmonary abscesses were seen most often on the right and in the upper lobes. They were usually the result of a major spill from the esophagus. Prolonged aspirations over many years gave rise to fibrosis which often was an end stage of pneumonitis or lung abscess. A typical roentgenographic picture was that of bilateral midzonal fibrosis, more extensive on the right and often sharply demarcated below by the fissures. There was very little disability. Lipoid pneumonia was the result of prolonged aspiration of oily substances such as mineral oil. The picture was similar to that of fibrosis with the additional feature of oily deposits. Collapse was due either to aspiration of a large bolus or to pressure by the enlarged esophagus. Clinically, the cases were arranged in 3 groups: (*1*) major pulmonary and minor dysphagic symptoms, (*2*) dysphagia with later development of pulmonary lesions, and (*3*) a few cases in which the symptoms appeared about simultaneously. There were 18 cases in group one. Cough was the chief symptom. Eight cases of "silent" dysphagia formed an important subgroup in which there was definite obstruction to normal deglutition but no subjective difficulty in swallowing. Group 2 contained 26 cases. In achalasia, the average duration prior to the appearance of pulmonary symptoms was 10 years. The dysphagia usually was minimal or periodic but regurgitation was common. In carcinoma and stricture, symptoms appeared sooner. In younger patients, bronchiectasis was more likely to appear than abscess. Acid-fast bacilli found in the sputum often were nonpathogenic types derived from food. In group 3, consisting of 4 cases, pulmonary and dysphagic symptoms appeared almost simultaneously.—*The pulmonary complications of dysphagia, J. R. Belcher, Thorax, March, 1949, 4: 44.*—(*A. G. Cohen*)

Lipoid Pneumonia.—The insidious development of pulmonary changes in individuals who take mineral oil for prolonged periods of time has been demonstrated. Faulty deglutition is not essential. A proliferative type of pneumonia develops and sometimes takes on the appearance of a circumscribed tumor. When the tissues are examined, free oil is found in the alveoli. The patients exhibit

remarkably few symptoms. In advanced cases, dyspnea and cough develop and the patients may have recurrent infections. The earliest roentgenographic lesion is a patchy infiltration similar to bronchopneumonia; at other times, the lesion has a hard appearance. Later the infiltrations fuse into a diffuse or circumscribed dense shadow. No hilar adenopathy develops. Early lesions clear up if the laxative habit is abandoned; more extensive lesions persist. The condition must be differentiated from other chronic pulmonary diseases, especially cancer. Besides evaluation of the clinical data, two tests are valuable. The first is the examination of the sputum for oil droplets. A fine paper applied to the surface of a collection of sputum will show grease spots. Sputum examined under the microscope after application of scarlet red will show the characteristic stain of the fat droplets. The other test is aspiration biopsy. Fat droplets can be demonstrated in the washings. The best treatment is prophylaxis. In advanced unilateral involvement, particularly with superimposed infection, surgical extrapation may be considered. The author reports 5 cases seen within a two year period in surveys performed on well adults.—*Pulmonary hazard of the ingestion of mineral oil in the apparently healthy adult, L. Schneider, New England J. Med., February 24, 1949, 240: 284.—(A. G. Cohen)*

Pneumonitis following Bronchography.—A case is described in which there was no immediate untoward reaction following bronchography. About fourteen days later, however, the patient developed fever and urticaria; roentgenography showed an extensive pneumonitis which had not been present earlier. All the symptoms gradually subsided. In cases of this sort, a history of familial or personal allergy usually is obtainable. Patients about to undergo bronchography should be questioned about previous reactions to iodides and also should have an intracutaneous test with diodrast. Even if these are negative, reactions may occur. If positive, the need for bronchography should be reviewed. The procedure may be done, nevertheless, but the patient should be encouraged to eliminate the iodized oil as soon as the test is completed and antihistaminic drugs should be given.—*Delayed pneumonitis and uriticaria following bronchography, H. E. Bass, New England J. Med., March 31, 1949, 240: 505.—(A. G. Cohen)*

Idiopathic Pulmonary Fibrosis.—There are numerous causes of pulmonary fibrosis but idiopathic fibrosis is a rare disease, the diagnosis of which requires the close cooperation of roentgenologist, pathologist, and clinician. The roentgenographic appearance is similar to that of fibrosis of various known causes and there is usually considerable emphysema when the condition is well-developed. The examination should include fluoroscopy to detect abnormal movement of the diaphragm, localized areas of emphysema, and paradoxical motion of the mediastinum. The early stages of the disease may not be distinguishable from numerous other processes. Later, there is an increase in the linear shadows, accompanied by a tendency to nodularity and some impairment in motion of the diaphragm. In the far advanced stage there is marked thickening of the strandlike shadows interspersed with areas of emphysema. In most cases the walls of emphysematous blebs are clearly demonstrated and there is definite limitation of motion of the diaphragm, especially on expiration. Paradoxical motion of the mediastinum, heart, and trachea is also generally noted. In one form of idiopathic fibrosis, the emphysema is out of proportion to the fibrosis. Cor pulmonale is often present but the heart shadow may be poorly seen because of the extensive fibrosis.—*Idiopathic pulmonary fibrosis: Roentgenologic findings, L. L. Robbins, Radiology, October, 1948, 51: 459.—(G. F. Mitchell)*

Interstitial Fibrosis of Lungs.—A 33 year old male printer complained of cough, dyspnea, palpitation, and fatigability. A chest roentgenogram showed fine infiltrates in both lower lobes. Dyspnea, cyanosis, and cough

increased and roentgenograms showed extension of the process throughout both lungs. The patient died with the signs of pulmonary insufficiency. Histologic examination of the lungs revealed thickening of the alveolar septums due to connective tissue proliferation and proliferation of the alveolar epithelial cells. This is a case of acute diffuse interstitial fibrosis of the lungs, which was first described by Hamman and Rich. The etiology of the disease is not known.—*Acute diffuse interstitial fibrosis of the lungs, B. P. Potter & I. E. Gerber, Arch. Int. Med., August, 1948, 82: 115.—(G. C. Leiner)*

Granulomatous Nocardiosis.—A new granulomatous disease entity caused by an unusual acid-fast organism is described. The patient was a white child, 34 months old, whose illness began with anorexia, nausea, vomiting, and progressive weight loss about four and one-half months before her death. Her course was afebrile. Shortly after the onset of her illness a mass was noted in the abdomen. An enlarged inguinal node was removed and showed complete alteration of its architecture with proliferation of the macrophages, the cytoplasm of which appeared foamy and granular. These cells contained massive numbers of acid-fast, bacilliform organisms resembling tubercle bacilli. The morphologic, cultural, and biochemical characteristics of this organism were those of a fungus but differed significantly from those of similar fungi. It was considered a new species of the family *Actinomycetaceae*, to which the name *Nocardia intracellularis* was given. In the child this organism producted a pure form of granulomatous inflammation characterized by phagocytosis of the pathogen by reticulo-endothelial cells with proliferation of these cells. In the spleen and lymph nodes the proliferation of macrophages displaced completely the normal structure. There was equilibrium between the organism and its host cell to the extent that massive intracellular parasitism constituted the most distinctive feature of the disease. Comparatively little necrosis occurred, and there was no response on the part of polymorphonuclear leukocytes or other inflammatory elements customarily found in the common infectious granulomas. *N. intracellularis* produces a nonlethal disease in guinea pigs, rats, and mice. It produces no lesions in chickens, rabbits, frogs, and goldfish. In the experimental animal, *N. intracellularis* provokes a response which differs sharply from the reaction in man. This difference is to be found in the comparatively extensive necrosis and relative paucity of intracellular organisms. The lesions heal rapidly in the experimental animal and are accompanied by the production of sensitivity of the tuberculin type.—*Pure granulomatous nocardiosis: A new fungus disease in man due to a hitherto undescribed organism, Nocardia intracellularis, n. sp., including a study of the biologic and pathogenic properties of this species, J. T. Cuttino & A. M. McCable, Am. J. Path., January, 1949, 25: 1.—(J. S. Woolley)*

Pulmonary Actinomycosis.—Actinomycosis is a rare disease, being most frequent among farm workers but occurring in both rural and urban communities. The commonest site of disease is the alimentary tract, especially in the ileocecal region, suggesting the oral route of infection; but the thorax is the primary site in one of 7 cases. The infecting organism in thoracic actinomycosis is usually anaerobic although the aerobic form is responsible for some cases. The thorax may be involved primarily, either by the inhalation of infected material or by penetration through the wall of the esophagus to the posterior mediastinum with spread to the lungs. It may be involved secondarily as a result of spread from cervical actinomycosis, retroperitoneal or hepatic infection, or by hematogenesis dissemination. When the lung is primarily involved, consolidation occurs usually in one of the lower lobes. If the visceral pleura is reached, pleural effusion is produced. The infection may then involve the thoracic wall with an empyema necessitatans. If the posterior mediastinum is infected, the thoracic vertebrae and adjacent ribs may be attacked. Cerebral abscesses

occur frequently as a complication of pulmonary actinomycosis following hematogenous dissemination. Early thoracic actinomycosis causes very slight symptoms such as cough or vague chest pain. Physical examination of the lungs may reveal signs of consolidation or of fluid. Later an abscess of the chest wall may develop. With long-standing infection, the symptoms are those of chronic suppuration with fever, anemia, cachexia, and finally amyloidosis. The diagnosis of actinomycosis is certain only when the characteristic sulfur granules have been seen or when the organism itself has been cultivated; secondary infection often makes the laboratory diagnosis difficult. The radiographic findings are varied, depending on the structures of the chest involved, and no characteristic changes may be expected. Three cases of pulmonary actinomycosis are presented. The first had a lung abscess of peculiar type which first suggested the diagnosis. The second case was characterized by multiple abscesses, prominent vascular markings, and dilated bronchi with abundant sputum. The third case had a mediastinal effusion. Aspirated fluid revealed the organism in the third case. All 3 cases responded favorably to penicillin.—*Pulmonary actinomycosis, S. F. Oosthuizen & N. H. Fainsinger, Brit. J. Radiol., March, 1949, 22: 152.—B. Hyde)*

Coccidioidomycosis.—A two- to five-year follow-up study of 20 veterans of World War II with various residual pulmonary lesions of coccidioidomycosis is presented with the case histories of 13 patients. All patients had lived for some time in the endemic area. The residual lesions were nodular densities, cavities, mottled infiltrations, fibrosis, pleural effusion, and calcifications. There was little or no change in the findings over the period of two to five years. The skin sensitivity to coccidioidin diminished slowly. In one case with disseminated lesions, the coccidioidin skin test was negative. Almost all patients were asymptomatic.—*Coccidioidomycosis: Persistence of residual pulmonary lesions, H. E. Bass, A. Schoner & R. Berke, Arch. Int. Med., December, 1948, 82: 519.—(G. C. Leiner)*

Coccidioidomycosis of Cattle.—Coccidioidomycosis was commonly found affecting the bronchial and mediastinal lymph nodes of cattle slaughtered under Federal inspection in Phoenix, Arizona. No lesions were found outside of the thoracic cavity and none were of sufficient extent to warrant condemnation of the carcass. The disease was present in 1.3 per cent of the slaughtered cattle. It is impossible to detect coccidioidomycosis in cattle on ante-mortem inspection and it is debatable whether the fungus gains entrance by inhalation or via the digestive tract. *Coccidioides immitis* is prevalent in Arizona where it is dry and dusty. Pathologically the affected lymph node has a bulbous appearance. Cross-section reveals few or numerous circular areas of pathologic tissue, each with a purulent center which may be white to light cream in color. Little or no change is noted in the surrounding lymphoid tissue.—*Coccidioidomycosis of cattle in Arizona, C. J. Prchal, J. Am. Vet. M. A., June, 1948, 112: 461.—(L. Hyde)*

Interstitial Pneumonia in Dogs.—Two canine cases of interstitial pneumonia with giant cells and inclusions are reported. The presence of both cytoplasmic and nuclear inclusions indicates the presence of distemper virus. This pneumonia is different from the typical exudative bronchopneumonia seen in 3 field cases of distemper. The interstitial pneumonia probably is a primary virus lesion while the exudative bronchopneumonia is due to secondary bacterial infection.—*Interstitial pneumonia with giant cells and inclusions, D. R. Cordy, J. Am. Vet. M. A., January, 1949, 114: 21.—(L. Hyde)*

Antimicrobial Therapy

Streptomycin and Streptokinase for Tuberculous Meningitis.—Necropsy of patients dying of tuberculous meningitis reveals a fibrinous exudate containing tubercle bacilli which streptomycin apparently does not

penetrate. It was decided to try streptokinase which is obtained from cultures of hemolytic streptococci. When injected alone intrathecally, this substance gave a pleiocytosis comparable to that produced by streptomycin. There were no untoward clinical effects. It was then given simultaneously with streptomycin sulphate in clinical cases of tuberculous meningitis. When streptomycin alone was used, there were 3 recoveries (21 per cent) in 14 cases. When the two were combined, there were 11 recoveries (58 per cent) in 19 cases.—*Streptomycin-streptokinase treatment of tuberculous meningitis, I. A. B. Cathie, Lancet, March 12, 1949, 1: 441.*—(*A. G. Cohen*)

Streptomycin for Extrapulmonary Tuberculosis.—Streptomycin was used in the treatment of extrapulmonary tuberculous lesions in 92 cases. There was significant pulmonary activity in only 2 cases; most of the others had healed residua. Many patients had multiple lesions making a total of 157. The earlier doses of streptomycin were as high as 3.0 Gm. a day. More recently, the dosage has been 1.0 Gm. daily for 42 days. The results of treatment were graded as excellent in 50, good in 36, and failure in 14 per cent. There were known recurrences in 8 per cent of the cured group. The results were best in cases with sinuses; closure occurred in 67 per cent in an average of 62 days; the other 33 per cent were improved. In bone and joint disease, the results were excellent in 35, good in 47 and failure in 18 per cent. In genito-urinary disease they were excellent in 52, good in 13 and failure in 15 per cent. In 74 per cent of postnephrectomy cases urine cultures were positive initially and turned negative. Poor renal function is not a contraindication if the drug is given in small doses. There was prompt arrest in 2 cases of lupus vulgaris. In 5 cases of adenitis the results were excellent in 2 and good in 3. In 3 cases of peritonitis the results were excellent in one and improved in 2. In 4 cases of mastoiditis the results were excellent in 2 and good in 2. In 4 cases of paraplegia secondary to spinal disease, there was complete cure in 2 and great improvement in one.—*Streptomycin in the treatment of extrapulmonary tuberculosis, K. Jellinek, New England J. Med., April 28, 1949, 240: 681.*—(*A. G. Cohen*)

Streptomycin for Tuberculous Endometritis.—A woman aged 26 was found to have a positive endometrial biopsy for tuberculosis. There was no evidence of tuberculosis elsewhere in the body. She received 0.5 Gm. of streptomycin twice daily for 129 days and was kept on bed rest. Following treatment, curettage showed no evidence of tuberculosis histologically or by culture.—*Streptomycin in the therapy of tuberculosis of the endometrium, A. Aronson & R. W. Dwight, New England J. Med., February 24, 1949, 240: 294.*—(*A. G. Cohen*)

Streptomycin for Tuberculous Enteritis.—In Veterans Administration hospitals 33 men have been treated with streptomycin for tuberculous enteritis. There were 29 white patients, 3 Negroes, and one Mexican. The average duration of their tuberculosis was nineteen months and all had far advanced pulmonary tuberculosis. Intestinal symptoms had been present four to six months prior to treatment. Intramuscular injections of 1.0 to 2.0 Gm. of streptomycin were given daily; at present 1.0 Gm. in 2 doses is recommended. Oral treatment was employed in 2 cases but four to six weeks elapsed before complete relief was obtained compared to one week when intramuscular treatment was used. Treatment usually was given for 60 to 120 days; 6 patients were treated only fourteen days. The drug uniformly relieved symptoms almost immediately. Increased appetite was noted first. In a few days there was loss of abdominal tenderness, rigidity, and distention. The temperature dropped to normal and there was a weight gain proportional to the previous weight loss. Tubercle bacilli disappeared from the sputum in only 8 cases. The pulmonary disease was not greatly improved in the

majority, although 3 patients received thoracoplasty after recovering from their intestinal disease. A fourteen day course of treatment was employed in 6 cases for the relief of symptoms only; the symptoms recurred in 2 cases. Of those receiving a longer course, 25 patients have been followed for an average of six and one-half months. One patient had 3 recurrences but for seven and one-half months has been symptom-free. His pulmonary disease also appears inactive. Two patients were operated on for acute appendicitis without developing a fecal fistula. One patient with tuberculous enteritis and epididymitis had had a resection of the ileum with a colostomy; he experienced marked relief. Roentgenograms and fluoroscopic reports of 17 patients showed abnormalities before treatment. The appearance returned to normal in 6 patients; 8 showed improvement with some residual deformity. Two patients showed marked residual deformity, one developed signs of a small bowel obstruction and one showed no roentgenographic change in spite of clinical improvement. From the radiological standpoint it was impossible to determine the ideal length of treatment. However, normal roentgenograms can be expected eventually if the abnormalities are primarily those of local irritation. Where ulceration has been deeper, more widespread, and of longer duration, there may be further distortion due to scar contraction.—*Streptomycin in the treatment of tuberculous enteritis: A report of thirty-three cases, E. E. Mason, W. W. Kridelbaugh, W. H. Crouch, & M. Ward, Am. J. M. Sc., January, 1949, 217: 28.*—(*G. F. Mitchell*)

Tuberculosis with Addison's Disease.—A 22 year old woman with tuberculous cavitation received pneumothorax and pneumonolysis despite which bilateral spread occurred. She had increasingly severe nausea, vomiting, and abdominal pain so that she became unable to retain even liquids. There was a rapid loss of 37 pounds. No tuberculosis of the gastrointestinal, urinary, and pelvic organs could be demonstrated and a diagnosis of Addison's disease was made. Treatment with adrenal cortex and streptomycin was followed by marked improvement within a week. The pneumothorax was maintained. The cavity closed and tubercle bacilli disappeared from the sputum. The Addison's disease may have been brought under control by the streptomycin.—*Active pulmonary tuberculosis together with Addison's disease, M. C. Cheney, J. A. M. A., April 16, 1949, 139: 1077.*—(*E. A. Rouff*)

Streptomycin-enhanced M. Tuberculosis.—Streptomycin greatly enhanced the growth of one strain of *Mycobacterium tuberculosis*. The organism was obtained from a 33 year old patient on the ninety-sixth day of treatment for advanced pulmonary tuberculosis which had been spreading constantly despite therapy. The organism grew very poorly and slowly in the control tube without streptomycin but luxuriantly in tubes of either Dubos-Davis or Lowenstein-Jensen medium containing 1.0 γ to 1,000 γ of streptomycin per cc. Growth at 1,000 was less striking but much greater than the control. This observation was duplicated in 5 of 7 trials. Another sputum sample was obtained four months later. The bacilli from this specimen would not grow in a medium without streptomycin but showed good growth on slants containing 1, 10, or 100 γ. of streptomycin per cc.—*Enhancement of growth of a strain of M. tuberculosis (var. hominis) by streptomycin, G. Spendlove, M. Cummings, W. Fackler, & M. Michael, Pub. Health Rep., September 3, 1948 63: 1177.*—(*S. Hadley*)

Streptomycin-resistant Tubercle Bacilli.—A large proportion of tuberculous mice, treated with amounts of streptomycin which permitted a relatively long survival time, yielded streptomycin-resistant tubercle bacilli. The more streptomycin administered the longer the survival time and also the greater the incidence of streptomycin-resistant strains of tubercle bacilli.—*Occurrence of streptomycin-resistant tubercle bacilli in mice treated with streptomycin, G. P. Youmans, E. H. Williston, & R. R. Osborne, Proc. Soc. Exper. Biol. & Med., January, 1949, 70: 36.*—(*F. B. Seibert*)

Neomycin.—Because of the disadvantages of streptomycin, a search has been continued among the Streptomyces for a compound which would be effective against the streptomycin-resistant bacteria, especially *M. tuberculosis*. Neomycin seems to be such an agent. It is a basic compound, most active in alkaline solution. It is soluble in water, insoluble in organic solvents, and is thermostabile. It is active against numerous gram-positive and gram-negative bacteria, especially *Mycobacteria*, but not against fungi. It displays similar activity against streptomycin-sensitive and streptomycin-resistant bacteria and considerable activity against *M. tuberculosis*. It has little or no acute toxicity to animals.—*Neomycin, a new antibiotic active against streptomycin-resistant bacteria, including tuberculosis organisms, S. A. Waksman & H. A. Lechevalier, Science, March 25, 1949, 109: 305.*—(*E. A. Rouff*)

Lupulon.—Lupulon, a fat-soluble antituberculous agent derived from hops, was effective *in vitro* in a dilution of 1:40,000. When given orally or intramuscularly it was active against experimental mouse infections of *M. tuberculosis*. Treatment with lupulon effected a reduction of approximately 4 to 1 in the numbers of acid-fast organisms in the lesions of animals infected with the H37Rv strain over those not treated. The LD_{50} on a single intramuscular injection was 600 mg. per Kg. in mice; on a single oral administration it was 1,500 mg. per Kg.—*Antituberculous activity and toxicity of lupulon for the mouse, Yin-Ch'ang Chin, H. A. Anderson, G. Alderton, & J. C. Lewis, Proc. Soc. Exper. Biol. & Med., January, 1949, 70: 158.*—(*F. B. Seibert*)

Salicylate – PAS Antagonism.—The bacteriostatic effect of para-aminosalicylic acid (PAS) was antagonized by high concentrations of salicylic acid. This effect of the salicylate was highly specific and not shared by related compounds. In one experiment it was shown that one mole of PAS was antagonized by 4 to 12 moles of sodium salicylate. One mole of para-aminobenzoic acid also abolished the effect of 4 moles of PAS. Pantothenic acid did not inhibit the tuberculostatic effect of salicylate.—*Antagonism between effects of p-aminosalicylic acid and salicylic acid on growth of M. tuberculosis, G. Ivánovics, Proc. Soc. Exper. Biol. & Med., March, 1949, 70: 462.*—(*F. B. Seibert*).

Laboratory Studies

Specific Serum Agglutination of Erythrocytes.—Red blood corpuscles can adsorb various substances and thereby can be rendered specifically agglutinable by an antibody directed against the substance adsorbed. The authors observed that the sera of tuberculous experimental animals and of tuberculous patients can agglutinate erythrocytes previously treated with aqueous extracts of tubercle bacilli or with products from their culture filtrate. Washed, packed sheep red cells were suspended in an excess of an isotonic, neutral, dialyzed solution of a crude polysaccharide fraction of tubercle bacilli. This was prepared by extracting the bacilli with aqueous dibasic phosphate solution after exhaustive extraction with 88 per cent phenol solution. When incubated with this extract, the red cells adsorbed the polysaccharide material. The red cells then were washed with isotonic saline solution and resuspended in 0.5 per cent concentration in saline for use as "sensitized cells" in the hemagglutination test. The serum to be tested was first heated to inactivate complement and then treated with approximately one-fifth of its volume of washed, packed, unsensitized sheep cells. This treatment was repeated in order to remove any nonspecific antibodies which might agglutinate unsensitized cells. The hemagglutination test was performed by adding to dilutions (1:8 to 1:1,024) of the treated serum an equal volume of the 0.5 per cent suspension of sensitized red cells. Appropriate controls were included in each test. The sera of rabbits injected with BCG showed varying potencies when tested. All showed some agglutination in a dilution of 1:80 and several agglutinated at 1:1,280. The sera of patients with active pulmonary tuberculosis gave agglutination in dilutions of 1:8 to 1:32. One patient with miliary tuber-

culosis had a titer of 1:256. None of the sera from nontuberculous individuals, including Wassermann-positive specimens, gave titers higher than 1:4. One sample of deglycerinated OT was found capable of sensitizing the sheep erythrocytes, showing that at least one substance responsible for sensitization is heat-stable and is present in the filtrate of cultures of mammalian tubercle bacilli. Experiments in which the carbohydrate and the protein fractions of bacillary extracts and culture filtrates were used to inhibit the specific hemagglutination demonstrated that the material responsible for the hemagglutination resides in the polysaccharide fraction; very small amounts of this fraction could be detected by this technique. Extracts of virulent and avirulent bacilli were equally effective in sensitizing the red cells. The antibody responsible for this hemagglutination test circulates in the blood of immunized animals and of human beings with active tuberculosis. The test exhibits a high degree of specificity and, in particular, does not give rise to any cross-reaction with Wassermann-positive sera as sometimes occurs in the case of the complement fixation reactions in tuberculosis. The specific hemagglutination reaction can be inhibited by adding the soluble reactive antigen to the serum before introducing the sensitized red cells into the system. Under these circumstances the soluble antigen, if present in sufficient amount, combines with its corresponding antibody and prevents it from agglutinating the sensitized erythrocytes. This inhibition test, when utilized together with the agglutination test proper, permits the quantitative detection of very small amounts of the sensitizing antigen. It will be interesting to test whether this technique permits the detection of specific antigen circulating *in vivo*.—*Specific serum agglutination of erythrocytes sensitized with extracts of tubercle bacilli, G. Middlebrook & R. J. Dubos, J. Exper. Med., November 1, 1948, 88: 521.*—(*J. S. Woolley*)

Nucleoproteins of Avian Tubercle Bacilli.—Crude nucleoprotein was best extracted from ether-washed, dry tubercle bacilli of the avian strain by grinding them for 30 minutes with glass powder and borate buffer at pH 8.3 and then shaking them in the cold with this buffer for two days. The extracts, after centrifuging, were dialyzed against water. Glycogen was removed by sedimentation at 31,000 g. and then the supernatant was again dialyzed and dried in a vacuum from the frozen state. It was further found that a nucleoprotein fraction flocculated around pH 4.0 but failed to precipitate in half-saturated ammonium sulfate at pH 6.3. It contained mostly desoxypentose nucleic acid. Attempts to isolate the nucleic acid from the nucleoprotein by means of proteolytic enzymes, disintegration by prolonged dialysis against molar sodium chloride, or precipitation with lanthanum nitrate were not successful. Cleavage with saturated sodium chloride was partially effective but it was more successful with sodium desoxycholate. Further purification was made by means of electrophoresis through which a nucleic acid fraction of 6.6 mg. was obtained. This fraction contained 12.9 per cent nitrogen and 7.6 per cent phosphorous.—*On the nucleoproteins of avian tubercle bacilli, E. Chargaff & H. F. Saidel, J. Biol. Chem., January, 1949, 177:* 417.—(*F. B. Seibert*)

Nucleic Acid of Avian Tubercle Bacilli.—Desoxypentose nucleic acids derived from avian tubercle bacilli and from yeast were found to contain the purines, adenine and guanine, and the pyrimidines, cytosine and thymine. No 5-methyl-cytosine could be detected in the nucleic acid of the tubercle bacilli. The sugar components of both nucleic acids, released by the hydrolysis of the enzymatically produced nucleosides, were found to be identical with the desoxypentose of thymus nucleic acid, *i.e.*, 2-desoxyribose. The pentose nucleic acid of the tubercle bacillus was shown to contain ribose.—*Microbial nucleic acids: The desoxypentose nucleic acids of avian tubercle bacilli and yeast, E. Vischer, S. Zamenhof, & E. Chargaff, J. Biol. Chem., January, 1949, 177: 429.*—(*F. B. Seibert*)

Test for Histoplasmosis.—A complement fixation test which had been studied previously in the guinea pig was used to test 300 human sera. The technique was essentially that of the Kolmer test. Of 9 proved cases of histoplasmosis 67 per cent had positive complement fixation reactions and 22 per cent showed doubtful reactions. Among 13 cases in whom the skin test for histoplasmosis had changed from negative to positive during a period of observation, 15 per cent of the complement fixation tests were positive and 77 per cent were negative. In a group of 36 persons who had unhealed pulmonary lesions with a positive histoplasmin skin test and a negative tuberculin, 17 per cent were positive, 11 per cent were doubtful, and 72 per cent were negative. A control group of 242 persons showed no positive reactions, 5.4 per cent doubtful reactions, and 94.6 per cent negative reactions. It is too early to draw definite conclusions but the test may prove to be useful in the study of histoplasmosis infections.—*A Complement fixation test for histoplasmosis: II. Preliminary results with human sera, M. L. Furcolow, J. L. Bunnell, & D. J. Tenenberg, Pub. Health Rep., February 6, 1948, 63: 163.*—(*S. Hadley*)

Pulmonary Anoxemia.—Studies of respiratory and circulatory functions were made in 18 patients with different degrees of pulmonary fibrosis and emphysema. Alveolar carbon dioxide tension was increased; alveolar oxygen tension was decreased. Due to unequal ventilation, the composition of the alveolar air is not uniform in the emphysematous lung. The ventilation rate was slightly increased, which may be due to cardiac decompensation or to the asphyctic stimulus. The total pulmonary capacity was slightly decreased. The average tidal air, the vital capacity, and the complemental air were less than normal, but the reserve air was about normal. The residual air and functional residual air were increased. The basal metabolic rate was increased in some cases. The oxygen capacity of the blood was increased in most cases. There was a coarse correlation between the degree of anoxia and the response of the bone marrow. The hemoglobin content per 100 cc. of red cells was lower than in normal subjects at sea level or at high altitude. Although the oxygen content of the arterial blood was slightly increased, oxygen saturation and pressure were below normal. The alkaline reserve was normal in whole blood, increased in plasma. The total carbon dioxide content and pressure of the arterial blood was increased; the pH was decreased. The difference between alveolar and arterial oxygen pressures was considerably increased but the difference between the carbon dioxide pressures was only slightly increased. Oxygen breathing caused a decrease in the ventilation and in the blood oxygen capacity, an increase in the difference between alveolar and arterial oxygen, a rise in the arterial carbon dioxide pressure, a decrease of the arterial pH, and a diminished heart rate. Breathing of carbon dioxide caused a smaller increase in the ventilation than in normal persons. An elevated venous pressure was found only when cardiac insufficiency was present. Ether and decholin circulation times were increased in most cases. The blood volume usually was increased due chiefly to an increase in the erythrocytes. The cardiac output was diminished in cases with cardiac insufficiency.—*Respiration and circulation in pulmonary anoxemia, A. C. Taquini, J. C. Fasciolo, J. R. E. Suarez & H. Chiodi, Arch. Int. Med., December, 1948, 82: 534.*—(*G. C. Leiner*)

Public Health and Epidemiology

Tuberculin Reactions in the Aged.—Tuberculosis tests were performed in 1947 on 257 unselected boarders at a Parisian home for the aged. Only 17 persons (6.6 per cent) had a negative reaction to a Mantoux test, using a 1:100 dilution of tuberculin; only 14 persons had a doubtful reaction. In the age group of 60 to 69 years, 4 per cent gave a negative reaction; in the group 70 to 79 years, 7 per cent; and in the group 80 to 102 years, 6.9 per cent had a negative reaction. This raises a question as to "anergy" due to old age.—*Les réactions tuberculiniques cutanées dans un hospice*

parisien de vieillards, Ch. Coury & P. Marland, Rev. de la tuberc., 1948, 12: 391.—(V. Leites)

Chest Roentgenograms in Tuberculosis.—The clinical significance of minor pulmonary infiltrates cannot be determined with accuracy from the chest roentgenogram and each case must be considered individually. The early diagnosis of tuberculosis depends upon the recognition and evaluation of nodular infiltrates usually located at the apex of the lung anterior to the plane of the first rib and slightly above it. The majority of these infiltrates heal, but small caseous areas unpredictably may produce fresh lesions by bronchiolar emboli. A single negative bacteriologic examination does not mean that dangerous numbers of bacilli will not be excreted later and frequent chest roentgenograms are probably the most reliable method for following minimal infiltrates. Tuberculosis undoubtedly spreads from apical foci with greater frequency in Negro than in white patients, but chest roentgenograms should be repeated every three months in any patient with a minimal infiltrate. Apical lesions in older males must be observed carefully since it is now apparent that these lesions may progress in individuals whose resistance is affected by metabolic, degenerative, and other changes accompaning advancing age. Annual roentgenograms of the chest should be a minimum recommendation for these patients. To feel falsely secure about any pulmonary infiltrate is dangerous to the patient and may expose others to months of contagion.—*The role of the chest roentgenogram in the evaluation of pulmonary tuberculosis, H. M. Payne, J. Nat. M. A., September, 1948, 40: 210.—(L. Hyde)*

Lung Cancer in Chromate Workers.—Workers in the chromate industry have been studied because of the high incidence of lung and respiratory tract carcinoma that has been noted among them. The group studied included 1,445 employees. The mean duration of exposure to chromates was 14.5 years. Of all the deaths in these men, 21.8 per cent were due to cancer of the respiratory system; this is 16 times the expected rate of 1.3 per cent. In 5 or 6 of the plants studied, the rates in the group over 50 years of age ranged from 20 to 70 times that for a comparable industrial group. One plant which handled only bichromate and chromic acid had no deaths due to carcinoma of the respiratory tract. This suggests that the monochromates may be the compounds responsible.—*Cancer of the respiratory system in the U. S. chromate-producing industry, W. Machele & G. Gregorius, Pub. Health Rep., August 27, 1948, 63:* 1114.—(*S. Hadley*)

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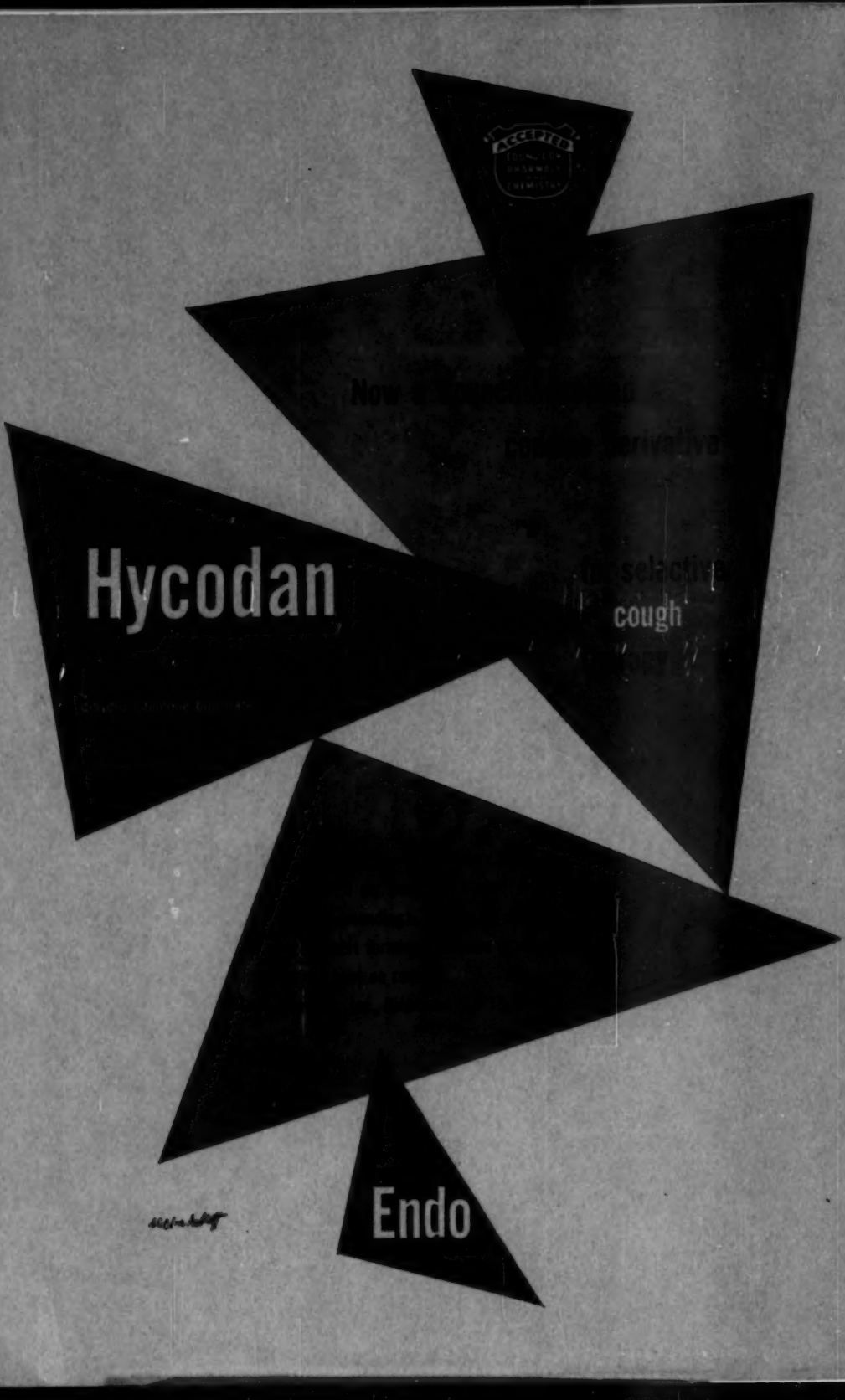
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